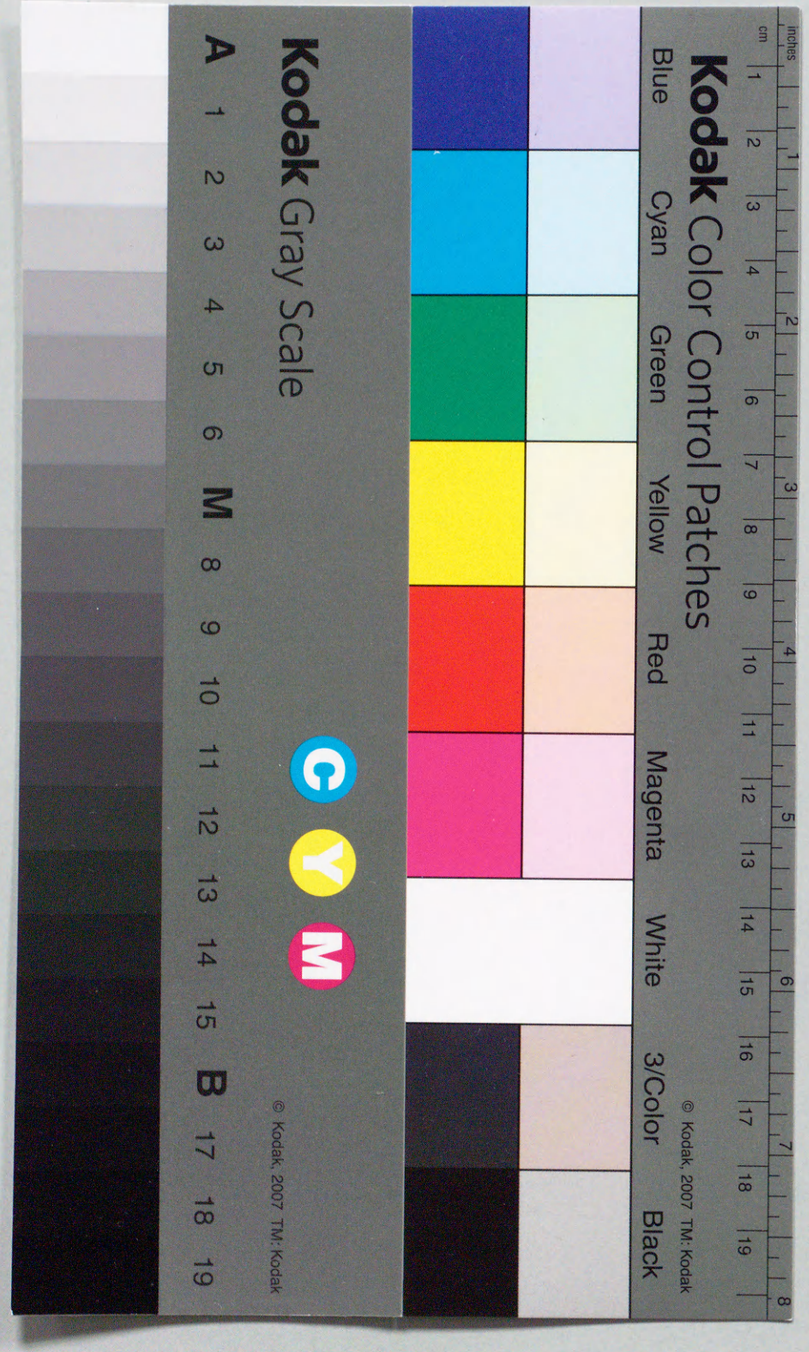
Enantioselective Electrocatalytic Oxidation on TEMPO-Modified Electrodes by Use of Chiral Base



Enantioselective Electrocatalytic Oxidation on TEMPO-Modified Electrodes by Use of Chiral Base

by

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1997

Dissertation

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(Bachelor of Pharmacy)

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List of Publication

1. "Enantioselective, Electrocatalytic Oxidative Couplings of Naphthol, Naphthyl Ether, and Phenanthrol on a TEMPO-modified Graphite Felt Electrode in the Presence of (-)-Sparteine (TEMPO = 2,2,6,6-tetramethylpiperidin-1-yloxyl)", *J. Chem. Soc., Chem. Commun.*, **1994**, 2535.
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2. "Enantioselective, Electrocatalytic Lactonization of Methyl-substituted Diols on a TEMPO-modified Graphite Felt Electrode in the Presence of (-)-Sparteine", *Chem. Lett.*, **1996**, 1043.
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3. "Enantioselective, Electrocatalytic Oxidation of Racemic Alcohols on a TEMPO-modified Graphite Felt Electrode by Use of Chiral Base (TEMPO = 2,2,6,6-tetramethylpiperidin-1-yloxyl) ", *Chem. Commun.*, **1996**, 2745.
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Yoshinori YANAGISAWA

Contents

CHAPTER ONE

Introduction

1-1 Intrinsic Characteristics of Electrochemical Reaction

An electrochemical reaction is intrinsically a heterogeneous reaction occurring in (the vicinity of) the interface between the electrode surface and an electrolytic solution. Double layer theory presented by Helmholtz[1] and Quincka[2] has been developed to apply to the electrode interface by many electrochemists such as Gouy, Chapman, Stern, Grahame and Frumkin.[3,4] When an electrode surface is put into contact with an electrolytic solution, the interface between them always forms a double layer of electric charge so as to compensate the electric charges at the electrode with the same quantity of electric charges distributed by the counter ions of electrolyte in the Helmholtz layer. Fig. 1 depicts a double layer structure and potential profile from a positively charged

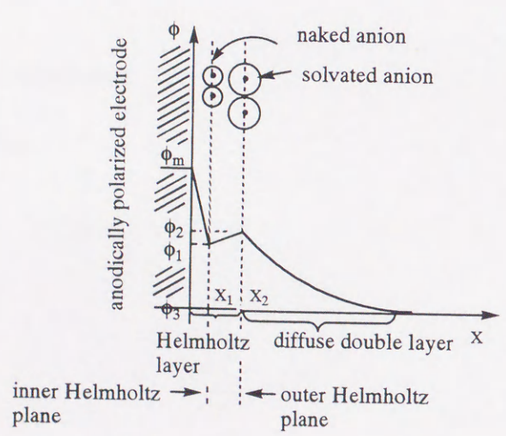


Fig. 1. Structure of electric double layer and potential profile in the vicinity of anodically polarized electrode (in the case of specific adsorption of anion to an electrode).

electrode into a bulk solution, accompanying specific adsorption by naked anions.[5] Electron transfer to/from substrates usually takes place from/to an electrode through a naked anion layer (the line connecting the center of the naked anions is called the inner Helmholtz plane) and, sometimes, adjacent solvated anion layer(s) (the line connecting the center of solvated anions is named the outer Helmholtz plane), though there are the cases in which substrates adsorb strongly at the electrode by themselves instead of specifically adsorbed anions. This specific adsorption of substrates at the surface of electrode will be effective for the stereocontrol of reactions of the substrates, as discussed later. The layer for the electron transfer is called the Helmholtz layer, whose thickness is ca. 10 Å or less even if a non-adsorbed (clean) electrode is used. On the other hand, the thickness of the diffuse double layer, which spreads to the outer direction of the Helmholtz layer, depends on the ionic strength, permittivity, and temperature of the electrolyte solution. The thickness of diffuse double layer increaes with increasing the permittivity and decreasing the ionic strength. The thickness is about 100 Å in 0.001 ionic strength and 10 Å in 0.1 ionic strength at 25°C in aqueous solution. Therefore, molecular level discussion is necessary to clarify the mechanism electrochemical reactions.

Since the beginning of polarographic investigations, specific adsorption of organic compounds to mercury surface has been observed and analyzed theoretically.[6,7] Most electrode reactions occur through adsorption of the reactive species at the electrode surface. Adsorption relates with catalytic action and, furthermore, is affected by the electric field or electrode potential. During electrolysis in underpotential, organic molecules are often desorbed from the electrode surface and the electrolysis can be continued.[8]

As can be understood from the structure of electrode interface, electrochemical methods have been considered to afford stereoselective and/or asymmetrical reactions, because electrochemical redox reactions take place in the heterogeneous electrode/ solution interface where an energetically highly oriented reaction field is established. One of the earliest studies concerning the stereochemistry of electrochemical reactions was made by Clemo and Smith in 1928.[9] They reduced *p*-dimethylaminobenzaldehyde at a cathode in aqueous sulfuric acid and separated one of the two diastereomeric glycols as a product. This kind of reactions can be realized by the oriented adsorption of reactive substrates to electrode, which cannot be attained by a homogeneous reaction system.[10] The adsorption of substrate to an electrode surface can be classified into physical adsorption and chemisorption. The former is induced mainly by van der Waals interaction and the effective distance for electron transfer is 10~15 Å from the electrode surface. The latter relies on weak chemical interactions. A value of adsorption enthalpy is about 25~40 kJ/mol the case of π- complex by polyaromatic compounds and the distance between the adsorbed substrate and electrode surface is estimated to be 3.5 Å.[11] The strength of adsorption depends on the type of solvents and electrode materials and is, in general, larger in aqueous solution or organic solvent-mixed aqueous solution than in non-aqueous solution. At a strong adsorption, the electronic state of adsorbed molecule might be changed. Nonaka has described that the important factors for stereocontrol in electrode reactions are 1) steric and polar factors, 2) conformational and configurational stabilities, and 3) thermodynamic and kinetic control.[12] These requirements for stereocontrol in electrochemical reactions have not been met fully, whereas a number of stereocontrolled electrode reactions have recently been reported individually.

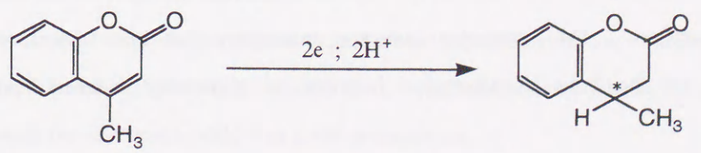
1-2 Historical Asymmetric Synthesis

Asymmetric synthesis is a very important area in organic chemistry. However, it must be noted that electrochemical asymmetric synthesis is immature compared with chemical, catalytic, and enzymatic methods, although much interest has arisen and many efforts have been made since the first report in this area by Grimshaw and coworkers in 1967.[13] They have carried out asymmetric reduction of activated olefins of prochiral coumarin derivatives in the presence of sparteine.[13,14] Tallec et al. proposed a chiral adsorption process as an asymmetry induction mechanism, in which optically active sparteine is adsorbed on the electrode surface.[15]

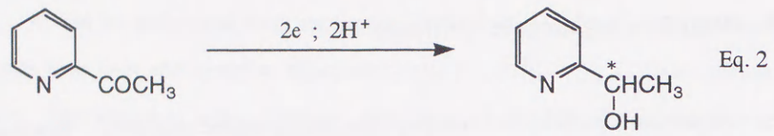
In the following section, the author classifies electro-chemical asymmetric syntheses reported so far based on the methodology used. The literature results are cited by paying attention to the asymmetry induction method and asymmetric yield.

A) Use of Chiral Adsorbents on Electrode

Grimshaw et al. reported 17% asymmetric yield in maximum in the reduction of prochiral coumarin derivatives (Eq. 1).[14] The asymmetric reduction of prochiral ketones to chiral alcohols has been investigated extensively by many researchers.[16-29] Kopilov et al. obtained 48% asymmetric yield for the reduction of 2-acetylpyridine as shown in Eq. 2.[20]



Eq. 1

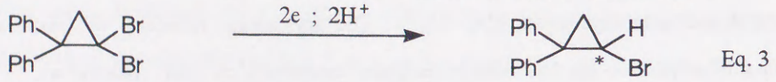


Eq. 2

More recently, Schafer et al. have performed cathodic reduction of 4-methyl-coumarin to 4-methyldihydrocoumarin and dihydrodimer in the presence of catalytic amounts of alkaloid (+)-yohimbine.[28,29] The enantiomeric excess (ee) of (*R*)-4-methyl-dihydrocoumarin was 12% with 57% chemical yield and the yield of dihydrodimer was 42%. They carried out an energy calculation based on AM1 and force field theory for the transition-state of a 4-methylcoumarin-(+)-yohimbine complex formed through hydrogen bonding.

The asymmetric reduction of C=N double bonds has been investigated using prochiral oximes.[26,27,30-32] The maximum asymmetric yield was reported to be 18%[27] and a mechanistic study was also reported.[26]

gem-Dihalides were also made subject to electrochemical asymmetric reduction into chiral monohalides,[33-35] and a maximum asymmetric yield of 44.3% has been reported for the reduction of 1,1-dibromo-2,2-diphenylcyclopropane (Eq. 3).[34]



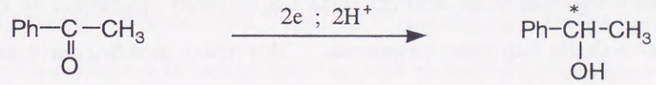
Eq. 3

Not only asymmetric yield of products but also their absolute configurations vary drastically with changing the operating variables such as cathodic potential, supporting electrolyte, solvent, pH, electrode material, substrate concentration, and other factors that influence adsorption. The asymmetry induction mechanism has been discussed theoretically on the basis of adsorption behavior of asymmetry inducers and

substrates.[36-39] Many inducers such as optically active amino acids have been used in addition to alkaloids.[40]

B) Use of Chiral Supporting Electrolytes

This method was first developed by Horner and Degner[41] in 1968 and has been applied to the asymmetric reduction of ketones[41-49] (Eq. 4) and imines[40,50,51] by using ephedrine hydrochloride as chiral supporting electrolyte. The maximum asymmetric yields reported for the former and the latter are 20%[46] and 8.95%,[51] respectively. On the other hand, the asymmetric yield for the hydrodimerization of acetophenone was 20.6% in the presence of ephedrine hydrochloride as chiral supporting electrolyte.[49]

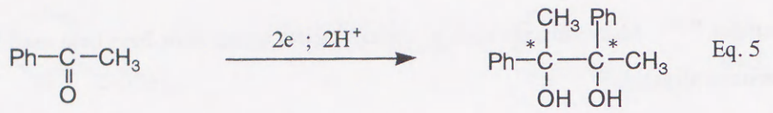


Eq. 4

The mechanism by which asymmetry is induced in the presence of chiral supporting electrolytes is still equivocal.[45,46,51] This type of asymmetric reduction seems less sensitive to the reaction conditions such as temperature, substrate concentration, etc. as compared with the high sensitivity of the electrode reactions using chiral adsorbents. However, it is a problem that the asymmetric yields are rather low in spite of using large amounts of asymmetric inducers, which play the role of supporting electrolyte.

C) Use of Chiral Media

Seebach and Oei reported the aysmmetric hydrodimerization of acetophenone in a chiral solvent ((*S*,*S*)-(+)-2,3-dimethoxy-1,4-bis(dimethylamino)butane) (Eq. 5),[52,53] in which the asymmetric yield was 6.4% in maximum.

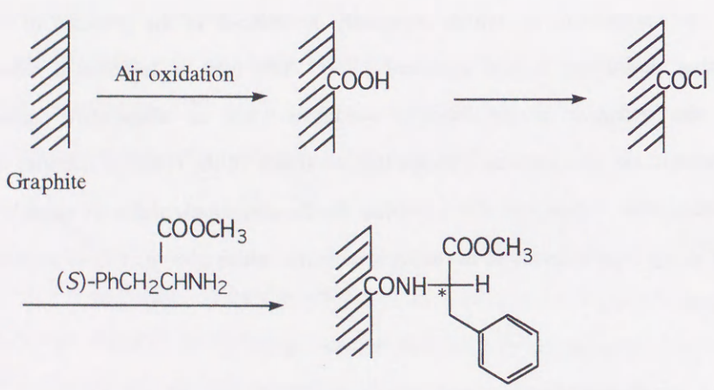


Eq. 5

The use of small amounts of chiral crown ethers[48] or cyclodextrins may have more potential, although any significant asymmetry induction has not been observed to date.

D) Use of Chiral Modified Electrodes

The fabrication of optically active material-modified electrode has inevitably derived from the asymmetric synthesis by chiral electrode adsorbents, because the adsorption of chiral compounds to the electrode surface is ultimately emphasized by an electrode modified covalently with chiral compounds. This type of modified electrodes



Scheme 1. Scheme for the preparation of (*S*)-phenylalanine-modified electrode.

have been firstly reported by Miller et al.[54,55] They have prepared an electrode chemically modified with (*S*)-phenylalanine (Scheme 1) for asymmetric reduction. The maximum asymmetric yield obtained was 14.5% in the reduction of 4-acetylpyridine. A similar electrode modified with (+)-camphoric acid was used for the asymmetric oxidation of *p*-tolyl methyl sulfide to the sulfoxide in 2.5% asymmetric yield.[56] However, no asymmetric induction could be observed in the reduction of carbonyl compounds on other cathodes modified with α-chiral amines.[57]

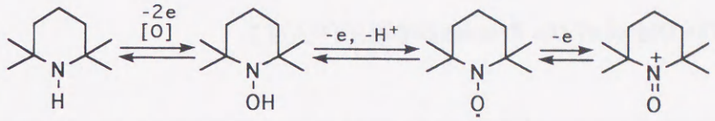
Nonaka et al. prepared a variety of electrodes coated with optically active poly(amino acid)s and applied them to both asymmetric reduction and oxidation.[58-63] The maximum asymmetric yields in the reduction of 4-acetylpyridine and oxidation of *p*-tolyl methyl sulfide were 43%[58] and 93%,[63] respectively. Though the asymmetric yield for the oxidation was satisfactorily high, the electrochemical reaction rate has not been reported. The mechanism of asymmetry induction was also discussed.[59]

Yamagishi and Aramata prepared a clay-coated electrode that incorporated optically active *tris*-(1,10-phenanthroline)ruthenium(II) into a montmorinite thin film.[64] In the oxidation of sulfides, a maximum asymmetric yield of 20% was obtained.

Simonet et al. prepared a new type of chiral electrode by forming a lamellar compound of graphite and optically active ammonium ions by electrochemical intercalation.[65] This electrode resulted in a maximum asymmetric yield of 9.3% in the reduction of *t*-butyl phenyl ketone to alcohol.

1-3 Poly(acrylic acid) Coated Graphite Felt Electrode Designed for Preparative Electrosynthesis

In Osa's laboratory, pioneering works have been done concerning the preparation of chemically modified electrode and its applications since the beginning of 1970s.[66,67] For asymmetric electrosynthesis, optically active tartaric acid-adsorbed Raney nickel electrodes have been developed.[68,69] A high current density can be passed on the Raney nickel electrode, but the maximum asymmetric yield for the reduction of methyl acetoacetate to *R*-(-)-methyl 3-hyroxylbutyrate did not exceed 30% on the (*R,R*)-(+)-tartaric acid-modified Raney nickel powder cathode.[69] Therefore, the study for asymmetric reaction using modified electrode had been left for future challenge. On the other hand, the construction of modified electrode for preparative electrosynthesis has been pursued for long time. The use of graphite felt (GF) as an electrode material was started in cooperative research with Bobbitt, The University of Connecticut, when he stayed in Sendai in 1987. After failure in the introduction of sufficient amounts of oxygenated reactive groups on the surface of GF for the purpose of preparative electrosynthesis, Akiba et al. have succeeded in the preparation of reactive surface by coating the GF surface with poly(acrylic acid) (PAA).[70] Later, mediator-modified GF electrodes which can be used for preparative electrosynthesis have been prepared by using 2,2,6,6-tetramethylpiperidin-*N*-yloxyl (TEMPO) as electron mediator for the oxidation of organic substrates.[71] The reversible redox system of TEMPO is shown in Scheme 2. The preparation of the TEMPO-modified electrode is briefly described here. The surface of GF electrode was coated with PAA by dip coating. The carboxyl groups in the PAA layer of the modified electrode was derivatized with 4-amino-TEMPO, cross-



TEMPO

Scheme 2. A reversible redox system based on TEMPO.

linked with hexamethylenediamine and the remainning free carboxyl groups were esterified with dibutyl sulfate.

The TEMPO-modified electrodes thus prepared were stable chemically and electrochemically and can be used for the oxidation of various kinds of organic compounds electrocatalytically. It should be noted that the modified GF electrodes made it possible to pass high electric current (~30 mA/cm^2), which was high enough to be employed for preparative electrolysis.

The TEMPO-modified GF electrodes have been used for the electrocatalytic oxidation of alcohols,[72] thiols,[73] naphthols,[74] and methylquinolines[71] in the presence of 2,6-lutidine in acetonitrile. 2,6-Lutidine was found to be the most effective accelerating agent or deprotonating agent for the oxidation of these compounds. The presence of water in the electrolysis medium lowered the reaction rate and/or the reaction activity, because the oxonium ion of TEMPO reacts with water. Therefore, it is necessary to remove water completely from the electrolysis system. The reactivity of TEMPO deteriorates gradually after repeated use. However, this is not a serious drawback of the system because the original activity of TEMPO can be restored easily by the treatment with peracid.

1-4 The Object of the Present Study

During the course of study on the effect of the type of bases on the deprotonation activity, the author has found that the cyclic voltammogams (CVs) of (*S*)-1-phenylethanol on the TEMPO-modified GF electrode are different significantly from those of (*R*)-isomer in the presence of chiral base of (-)-sparteine in place of 2,6-lutidine. This phenomenon suggested strongly that the TEMPO-modified GF electrode can be used for enantioselective electrocatalytic reactions. A detailed study on the voltammetric behavior of (*S*)- and (*R*)-1-phenylethanol revealed that the enantioselective oxidation of the racemic alcohol proceeds in the presence of chiral base. As an extension of this finding, in the present study, the author has applied this enantioselective electrode system to oxidative coupling reaction of naphthols, oxidative lactonization of substituted diols, and oxidation of racemic alcohols. Furthermore, the author tries to elucidate the reaction mechanism based on experimental evidence.

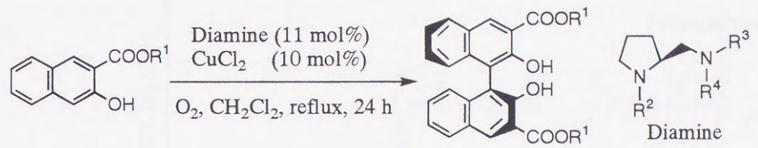
CHAPTER TWO

Electrocatalytic Oxidative Coupling of Naphthols and Phenanthrol in the Presence of (-)-Sparteine

2-1 Introduction

Direct coupling reaction of naphthols has been considered to be important from the viewpoint of electrochemical reactions. However, only few electrochemical coupling methods have been reported, because direct electrolysis of naphthols deposits a polymer film on the surface of electrodes which halts the reaction.[75] In 1993, Osa and coworkers have reported that 2-naphthol,[74] 2-methoxynaphthalene[74] and 2- and 4-methylquinolines[71] are quantitatively oxidized to the corresponding binaphthyls and biquinoyls in more than 90% current efficiency on a graphite felt (GF) electrode modified with 4-amino-2,2,6,6-tetramethylpiperidin-N-yloxy (4-amino-TEMPO). It is well known that 1,1'-binaphthol derivatives possess their axial dissymmetry and molecular flexibility.[76] In their investigations, however, enantioselectivity of the produced binaphthols has not been observed.

On the other hand, since optically pure binaphthyls such as (*S*)-(-)- or (*R*)-(+)-2,2'-dihydroxy-1,1'-binaphthyl have been utilized in a variety of synthetic reactions to induce chirality,[77] much attention has been paid to their synthesis. Optically active binaphthyls have been synthesized by three enantioselective routes : a) an intramolecular Ullmann coupling,[78] b) a nucleophilic aromatic substitution,[79,80] and c) an oxidative dimerization of 2-naphthols with copper(II) amine complexes as oxidants.[81-86] In the recent paper,[86] Nakajima et al. have described that asymmetric aerobic coupling of 3-hydroxy-2-naphthoate using copper complex prepared in situ from chiral diamine and cuprous chloride as catalyst afforded binaphthol derivatives in 73% ee as shown in Eq. 6. However, the reactions catalysed by such catalyst system suffered from the limitation arising from the effects of the type and position of substituents of naphthols and thus 2-naphthol did not give binaphthyl.



Eq. 6

In this chapter, the author describes highly enantioselective oxidative coupling of 2-naphthol (**1**), 2-methoxynaphthalene (**2**), and 10-phenanthrol (**3**) on the TEMPO-modified GF electrode in the presence of reaction accelerator or deprotonation agent such as (-)-sparteine.

2-2 Experimental

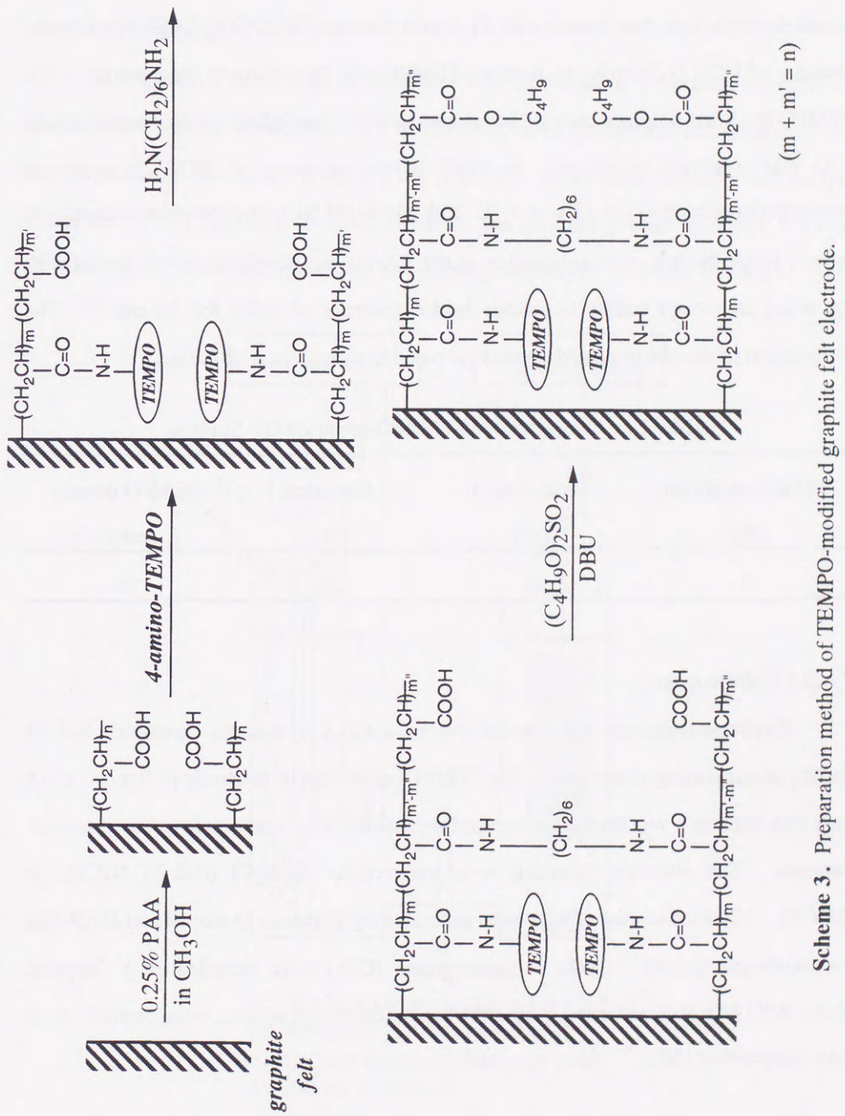
Materials.

Graphite felt (GF, National Electric Carbon Corp., WDF, surface area 0.7 m^2/g) was kindly gifted by Prof. J. M. Bobbitt, The University of Connecticut.

Dry poly(acrylic acid) (PAA) of average molecular weight of 1,400,000 was prepared by freeze-drying a 25% aqueous solution obtained from Wako Pure Chemical Industries. 4-Amino-2,2,6,6-tetramethylpiperidin-1-yloxyl (4-amino-TEMPO) was purchased from Aldrich Chemical Company. Hexamethylenediamine, dicyclohexylcarbodiimide (DCC), di-*n*-butyl sulfate, and 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) were purchased from Tokyo Chemical Industry. Acetonitrile (CH_3CN, guaranteed reagent, Nakarai Tesque) was stored over molecular sieves (4Å, 1/16) for 24 h and then distilled in the presence of $CaCl_2$. Sodium perchlorate ($NaClO_4$, guaranteed reagent, Nakarai Tesque) was recrystallized from CH_3OH. Other solvents such as acetone, methanol, diethyl ether and *N,N*-dimethylformamide (DMF) were purified by the methods described in the literature.[87] The chemical reagents used for macroelectrolysis were of reagent grade.

Preparation of TEMPO-modified Graphite Felt Electrode.

The TEMPO-modified electrode was prepared according to the reported procedure.[71] A preparation procedure of the modified electrode is described in Scheme 3. GF electrode (5.0 x 2.0 x 0.5 cm^3) was coated with PAA by the treatment with 0.25% PAA methanol solution: the electrode was immersed in the PAA solution for 5 min and then air-dried. The thickness of PAA layer thus prepared was calculated to be ca. 40 nm based on the gravimetric measurement of the PAA-coated electrode. This PAA



Scheme 3. Preparation method of TEMPO-modified graphite felt electrode.

coated electrode was then treated with 41.6 mM 4-amino-TEMPO in DMF (5 ml) in the presence of DCC (1.2 equiv. to 4-amino-TEMPO) for 72 h at room temperature. The TEMPO-modified polymer layer of the electrode was crosslinked by the treatment with 6.94 mM hexamethylenediamine in DMF in the presence of DCC (2 equiv. to hexamethylenediamine) for 12 h at 4 °C and additional 60 h at room temperature. In order to block the free carboxyl residues in the PAA layer, the electrode was treated with 0.8 mmol di-*n*-butyl sulfate in acetone in the presence of DBU for 30 min.[88] The composition of the electrode surface thus prepared is summarized in Table 1.

Table 1. Composition of TEMPO-modified GF Surface.

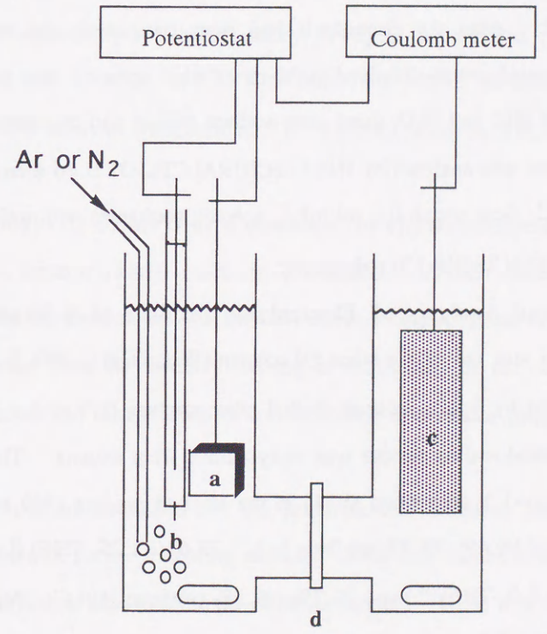
TEMPO-modified (%)	Cross-linked (%)	Butylated (%)	TEMPO density (μmol/cm^3)
64	16	20	24

Cyclic Voltammetry.

Cyclic voltammetry was carried out in a CH_3CN solution containing 0.2 M $NaClO_4$ as supporting electrolyte. The TEMPO-modified GF electrode (1.0 x 1.0 x 0.5 cm^3) was used as a working electrode, and a platinum wire was employed as a counter electrode. The electrode potentials were referred to Ag/AgCl (0.2 M $NaClO_4$ in CH_3CN). Cyclic potential sweeps were generated by a Hokuto Denko Model HAB-151 potentiostat/galvanostat. Cyclic voltammograms (CVs) were recorded on a Graphtec Model WX1200 X-Y recorder. All electrochemical measurements were carried out at room temperature (20 ± 2 °C).

Macroelectrolysis.

A preparative electrolysis of substrates was performed at a constant potential on the TEMPO-modified GF electrode in CH_3CN using an H type divided cell separated by a cationic-exchange membrane (Nafion 117) (Fig. 2). In a typical example, the anolyte contained 5 mmol substrate, 2 mmol tetralin as gas chromatographic standard, 5 mmol (-)-sparteine and 1 mmol $NaClO_4$ as a supporting electrolyte in a total volume of 5 ml.



a : Working electrode (1.0 x 1.0 x 0.5 cm^3)
b : Reference eletrode (Ag/AgCl)
c : Counter electrode (Platinum plate)
d : Nafion membrane

Fig. 2. Schematic representation of two-compartment cell for electrolysis.

The catholyte was 5 ml CH_3CN solution containing 1 mmol $NaClO_4$. The controlled potential electrolysis was carried out at +0.6 V *vs.* Ag/AgCl under an argon atmosphere. The size of the modified GF anode was 1.0 x 1.0 x 0.5 cm^3. The anolyte was sampled at appropriate intervals for GC analysis (Unicarbon A-100 3 m / column temp. 220 °C, inj. temp. 240 °C, det. temp. 260 °C) and HPLC (CHIRALCEL-OT 0.46 ϕ cm x 25 cm / column temp. 30 °C, flow speed: 0.5 ml·min^{-1}, solvent: methanol). The end point of electrolysis was usually determined by a disappearance of the substrate by GC or by diminishing current. After the electrolysis had been completed, the anolyte was evaporated and the residue was dissolved in 30 ml of ethyl acetate. The mixture was washed with 0.1 M HCl and H_2O, dried over sodium sulfate and concentrated. The purity of the products was analyzed by HPLC (CHIRALCEL-OT 0.46 ϕ cm x 25 cm / column temp. 30 °C, flow speed: 0.5 ml·min^{-1}, solvent: methanol) and optical rotation was measured by a JASCO-DIP-370 polarimeter.

Isolation and Analysis of Electrolysis Product of 2-Naphthol (1): The reaction mixture was fed onto a silica gel column (Wako Gel C-200, 3 cm ϕ x 50 cm), and fractionated by light petroleum-diethyl ether mixture (1:1 v/v). The eluted solution was evaporated and the residue was recrystallized from toluene. The purity of (*S*)-(-)-2,2'-dihydroxy-1,1'-binaphthyl (***S*-4**) in the isolated product (669 mg, 93.6% yield) was found to be 99.4% (98.5% ee) from $[\alpha]_D^{20}$ -33.6° (*c* 1.25, THF) ($[\alpha]_D$ of pure compound is -34° (*c* 5.0, THF)[83]) and 99.7% (99.5% ee) from HPLC. Mp: 209-212 °C (lit.[83] mp: 210-214 °C).

Isolation and Analysis of Electrolysis Product of 2-Methoxy-naphthalene (2): The reaction mixture was fed onto a silica gel column (Wako Gel C-200, 3 cm ϕ x 50 cm), and fractionated by diethyl ether-ethyl acetate mixture (1:1 v/v). The eluted solution was evaporated and the residue was recrystallized from chloroform.

The purity of (*S*)-(-)-2,2'-dimethoxy-1,1'-binaphthyl (***S*-5**) in the isolated product (716 mg, 92.3% yield) was found to be 91.4% ee from $[\alpha]_D^{20}$ -74.2° (*c* 1.25, THF) ($[\alpha]_D^{21}$ (*c* 1, THF) of pure compound is -79.5°[89]) and 93.6% ee by HPLC.

Isolation and Analysis of Electrolysis Product of 10-Phenanthrol (3): The reaction mixture was fed onto a silica gel column (Wako Gel C-200, 3 cm ϕ x 50 cm), and fractionated by light petroleum-diethyl ether mixture (1:1 v/v). The eluted solution was evaporated and the residue was recrystallized from toluene. The purity of (*S*)-(-)-10,10'-dihydroxy-9,9'-biphenanthryl (***S*-6**) in the isolated product (881 mg, 91.2% yield) was found to be 97.9% ee from $[\alpha]_D^{20}$ -69.5° (*c* 1.25, $CHCl_3$) ($[\alpha]_D^{23}$ ($CHCl_3$) of 98% purity of compound is -71°[81]) and 98.3% ee by HPLC.

The advantages of TEMPO as a mediator for electrocatalytic oxidation.

In the electron transfer reactions on a mediator-modified electrode coated with a polymer layer, the electron transfer between electrode and substrate usually proceeds via electron transfer from the mediator existing in the vicinity of the electrode surface to electrode surface and charge transfer from mediator to mediator (intermolecular charge transfer).

The optimum mediators for the preparation of modified electrode should be organic compounds for the following reasons. First, they can be covalently attached to the polymer which is deposited on the electrode surface. Thus, it is easy to immobilize the mediators on the electrode surface strongly. Another point is that, due to the structural versatility of organic compounds, the chemical structure of the organic mediators can be regulated to give a high degree of regioselectivity and perhaps even stereoselectivity. Unfortunately, very few mediators have been reported which are

suitable to this purpose. In this study, the author uses TEMPO derivatives as mediators for oxidation reactions.

Since TEMPO derivatives were synthesized in 1962 as super stable radical species,[14] various nitroxyl radicals have been prepared and utilized mainly for ESR study.[15] Recently the chemical behaviors of these compounds, especially redox reactions, have attracted the attention of many chemists, and their interesting features have been gradually clarified in several papers. TEMPO constructs the reversible redox system as shown in Scheme 2.[16]

2-3 Results and Discussion

The cyclic voltammograms of **1** (0.1 M) on TEMPO-modified GF electrode with and without 0.01 M (-)-sparteine as chiral alkaloid base are shown in Fig. 3. The TEMPO-modified GF electrode itself exhibited well defined reversible redox peaks at

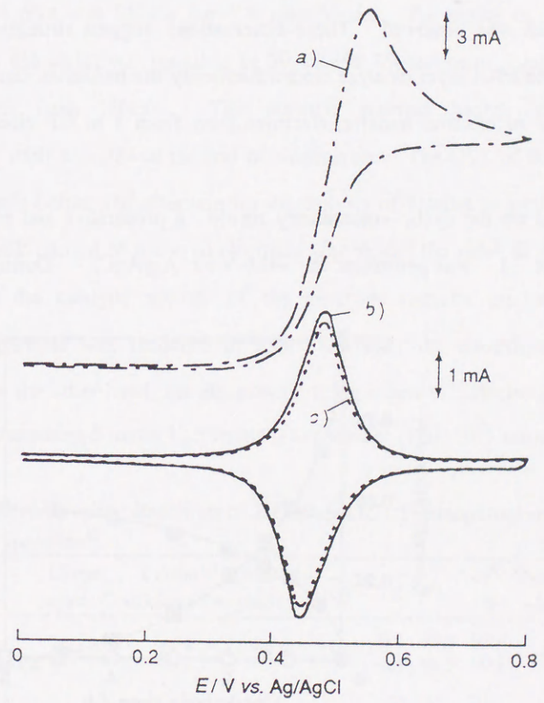


Fig. 3. Cyclic voltammograms of TEMPO-modified GF electrode (1.0 x 1.0 x 0.5 cm^3) in 0.2 M $NaClO_4/CH_3CN$ at a scan rate of 10 mV/s. Curve *a*) in the presence of 10 mM 2-naphthol and 10 mM (-)-sparteine, curve *b*) in the absence of both 2-naphthol and (-)-sparteine, curve *c*) for the electrode after one run of macroelectrolysis.

+0.44 ~ +0.46 V *vs.* Ag/AgCl in the absence of **1** and (-)-sparteine, suggesting that TEMPO retains its redox activity in the PAA layer. In other words, the electron transfer reaction procceds between the TEMPO residues and GF through the PAA layer smoothly and reversibly. In the presence of 10 mM **1** and 10 mM (-)-sparteine, the oxidation peak current at +0.55 V *vs.* Ag/AgCl was highly enhanced, being 23.4 mA as compared with the value of 2.8 mA in the absence of (-)-sparteine. Another feature is that no re-reduction peak was observed. These observations suggest strongly that the TEMPO residues in the PAA layer catalyze electrochemically the oxidation reaction of **1**. From the viewpoint of electron transfer, electrons flow from **1** to GF electrode via TEMPO residues.

Based on the cyclic voltammetry results, a preparative and controlled potential electrolysis of **1** was performed at +0.6 V *vs.* Ag/AgCl. During the electrolysis,

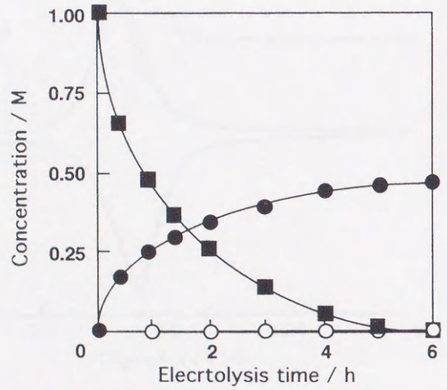


Fig. 4. Macroelectrolysis of 2-naphthol on TEMPO-modified GF electrode (1.0 x 1.0 x 0.5 cm^3) in the presence of (-)-sparteine. ■: 2-naphthol, ●: (*S*)-(-)-2,2'-dihydroxy-1,1'-binaphthyl, ○ : (*R*)-(+)-2,2'-dihydroxy-1,1'-binaphthyl.

aliquots of sample for GC and HPLC analysis were taken from the reaction mixture at appropriate intervals.

The time course of the electrolysis of **1** is shown in Fig. 4. 5 mmol **1** (1 M concentration) reacted completely in about 6 h to yield **4**. The current efficiency, isolated yield, and ee in the electrolysis are collected in Table 2. The current efficiency for the formation of ***S*-4** was 88.8% for 6 h electrolysis. The purity of ***S*-4** in the isolated product (93.6% yield) was found to be 99.4% (98.8% ee) from polarimetry and 99.7% (99.5% ee) from HPLC. The turnover number based on TEMPO (product/TEMPO in mol) was 384 at the end of electrolysis. The CVs of the TEMPO-modified GF electrode before and after use for electrolysis of **1** were shown in Fig. 3. It is clear that the peak current of the used electrode was almost the same as that of new one, showing that the catalytic activity of the electrode remains unchanged after electrolysis. (-)-Sparteine was recoverd in 95% yield after the electrolysis without decomposition. On the other hand, the electrolysis using a bare GF electrode in 0.2 M $NaClO_4$ / CH_3CN containing 5 mmol **1**, 5 mmol (-)-sparteine and 0.5 mmol 4-acetyl-

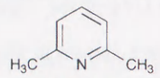
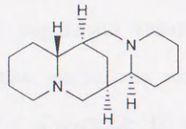
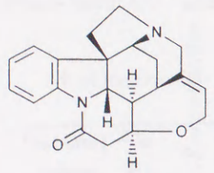
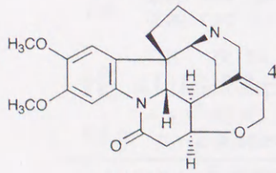
Table 2. Oxidative Coupling Reactions of 2-Naphthol to 1,1'-Binaphthol in the Presence of (-)-Sparteine[a)]

Method	Charge passed / C	Current efficiency / %	Isolated yield / %	$[\alpha]_D^{20}$	*R* : *S*[d)]	ee[d)] / %	Turnover[e)] number
electrocatalytic on TEMPO-modified GF	513.2	88.8	93.6	-33.6°	0.6 : 99.4 0.3 : 99.7	98.8 99.5	384
electrocatalytic on bare GF[b)]	519.9	92.4	93.4	-3.4°	45 : 55 44.5 : 55.5	10 11.1	9.3
reagent oxidation[c)]	—	—	90.2	-2.0°	47 : 53 46.7 : 53.3	6 6.7	0.9

a) the presence of 5 mmol 2-naphthol and 5 mmol (-)-sparteine in each reaction, b) 0.5 mmol 4-acetylamino-TEMPO in 5 ml of 0.2 M $NaClO_4$ / CH_3CN, c) 5 mmol oxoammonium tosylate of 4-acetylamino-TEMPO in 5 ml of CH_3CN, 24 h, d) upper row: obtained by polarimeter (20°C, *c* 1.25, THF), lower row: obtained by HPLC, e) calculated from 1,1'-binaphthyl (mol) x 2 / TEMPO (mol).

acetylamino-TEMPO yielded ***S*-4** with only 10% ee (92.4% current efficiency). A reagent oxidation of **1** with 5 mmol oxoammonium tosylate of 4-acetylamino-TEMPO[90] dissolved in acetonitrile afforded ***S*-4** in 90.2% yield and 6% ee.[91] These results are summarized in Table 2. It is clear that highly enantioselective coupling reaction of **1** proceeds only on the TEMPO-modified electrode.

Table 3. Effect of Added Bases in Electrocatalytic Oxidation of 2-Naphthol

Base	Charge passed / C	Current efficiency / %	Isolated yield / %	$[\alpha]_D^{20}$	$R : S$[a]	ee[a] / %	Turnover[b] number
 2,6-lutidine	504.2	95.7	98.6	0°	50 : 50 50 : 50	0 0	404
 (-)-sparteine	513.2	88.8	93.6	-33.6°	0.6 : 99.4 0.3 : 99.7	98.8 99.5	384
 (-)-strychine	512.4	90.2	95.8	-14.9°	28.1 : 71.9 27.6 : 72.4	43.8 44.8	393
 (-)-brucine	484.6	92.3	92.7	+7.3°	60.8 : 39.2 61.4 : 38.6	21.6 22.8	380

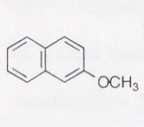
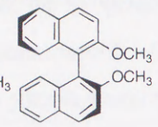
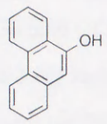
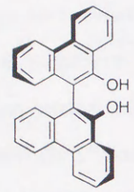
a) upper row: obtained by polarimeter (20°C, *c* 1.25, THF), lower row: obtained by HPLC, b) calculated from 1,1'-binaphthyl (mol) x 2 / TEMPO (mol).

The present electrooxidative coupling reaction requires base as deprotonation agent, as shown by the cyclic voltammetry. More important is the fact that the enantioselectivity of the reaction relies upon the chirality of the base bacause no other chiral source is involved in the reaction system. Therefore, the type of chiral base should be a crucial factor in determining the enantioselectivity of the reaction. The effects of the type of chiral bases are summarized in Table 3. Primary amines cannot be used as base in this reaction because TEMPO is known to react directly with primary amine such as amphetamine.[92] Therefore, the author has examined the enantioselective coupling reaction by use of chiral tertiary amines such as (-)-strychnine and (-)-brucine. In the case of (-)-strychnine, the chemical yield of ***S*-4** in the isolated product (95.8% yield) was found to be 71.9% (43.8% ee) from polarimetry and 72.4% (44.8% ee) from HPLC (90.2% current efficiency). In the case of (-)-brucine, the enantioselectivity of the product was reversed and ***R*-4** was produced in the isolated yield of 92.7% (92.3% current efficiency). It had the optical purity of 60.8% (21.6% ee) from polarimetry and 66.4% (22.8% ee) from HPLC. The results suggest that the structure of chiral base determines the enantioselectivity of the reaction probably due to a different type of conformation of intermediate composed of **1**, TEMPO, and base in the PAA domain.

The results of electrolysis for **2** and **3** performed using (-)-sparteine under the same conditions as for **1** are shown in Table 4. The coupling products showed high enantiopurity: 91.4% ee by polarimetry and 93.6% ee by HPLC for ***S*-5** from **2** and 97.9% ee by polarimetry and 98.3% ee by HPLC for ***S*-6** from **3**. In both cases, current efficiency was satisfactorily high (ca. 90%) and the turnover number was > 370.

The reaction mechanism of the present system seems to have a similarity to that of the reactions catalyzed by Cu-chiral amine complex which was described in category c) in chapter 2-1, because the former involves an electron transfer process between substrate

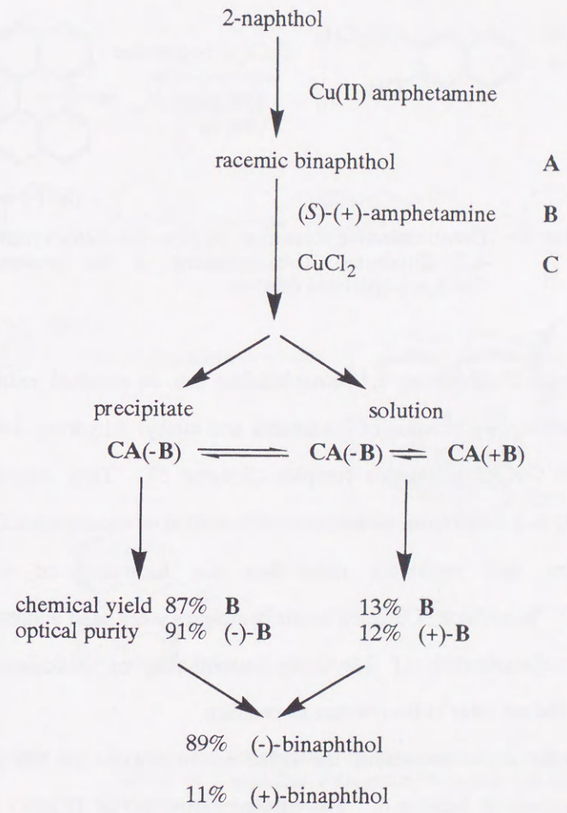
Table 4. Stereoselective, Electrocatalytic Coupling Reactions of 2-Methoxynaphthalene and 10-Hydroxyphenanthrene on TEMPO-modified GF Electrode in the Presence of (-)-Sparteine[a)]

Substrate	Product	Charge passed / C	Current efficiency / %	Isolated yield / %	$[\alpha]_D^{20}$	ee[b)] / %	Turnover number
		521.5	91.0	92.3	-74.2°	91.4 93.6	378
		531.3	89.6	91.2	-69.5°	97.9 98.3	374

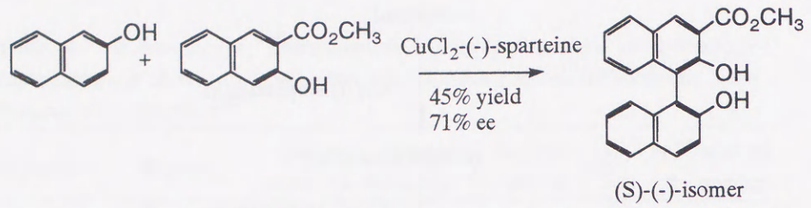
a) carried out in the same electrolysis conditions as for 2-naphthol, b) upper row: obtained by polarimeter (20°C, *c* 1.25, THF), lower row: obtained by HPLC.

and electrode and the latter contains the similar process between Cu metal and substrate as a key step. Brussee et al. have reported that, in the oxidation of **1** with copper(II)-chiral amine complexes, **4** is formed enantioselectively by selective precipitation of copper(II)-(+)-amphetamine-(*S*)-(-)-binaphthyl complex followed by a simultaneous enantiomerization of (+)-binaphthol when (+)-amphetamine is used.[82)] They proposed a second order transformation mechanism (Scheme 4).

It is important to determine which mechanism is predominant in the author's system: a direct mechanism or second order transformation mechanism. (*R*)-Binaphthyl was not enantiomerized on the electrode kept at + 0.6 V *vs.* Ag / AgCl in CH_3CN in the presence of (-)-sparteine ($[\alpha]_D^{20}$ of (*R*)-binaphthyl (+33.8°) remained unchanged after 0.2 Coulomb of electric charge had been passed or after 24 h). Furthermore, no enantiomerization of (*R*)-binaphthyl was observed in the presence of oxoammonium tosylate of 4-acetylamino-TEMPO. These results suggest that the asymmetric induction by the present electrochemical method does not arise from second order transformations but stems from a direct electrochemical reaction. Smrcina et al. reported that (*S*)-(-)-3-



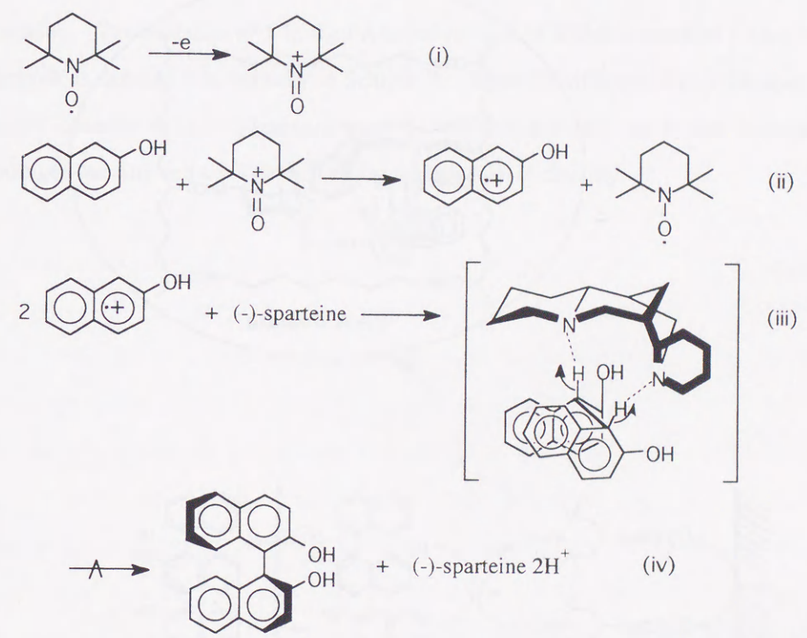
Scheme 4. Second order transformation mechanism.



Scheme 5. Enantioselective formation of (*S*)-(-)-3-methoxycarbonyl-2,2'-dihydroxy-1,1'-binaphtalene in the presence of $CuCl_2$-(-)-sparteine catalyst.

methoxycarbonyl-2,2'-dihydroxy-1,1'-binaphthalene can be obtained enantioselectively by the oxidative coupling reaction of 2-naphthol and methyl 3-hydroxy-2-naphthoate in the presence of $CuCl_2$/(-)-sparteine complex (Scheme 5). They described that the enentioselectivity is derived from the preferential formation of squareplaner Cu complexes with (-)-sparteine and naphthols rather than the formation of tetrahedral Cu complexes. [83,84] In addition, Cu-chiral amine complexes were used successfully for the enantioselective dimerization of 3-hydroxy-2-naphthoate by Nakajima et al [85,86] However, they did not refer to the reaction mechanism.

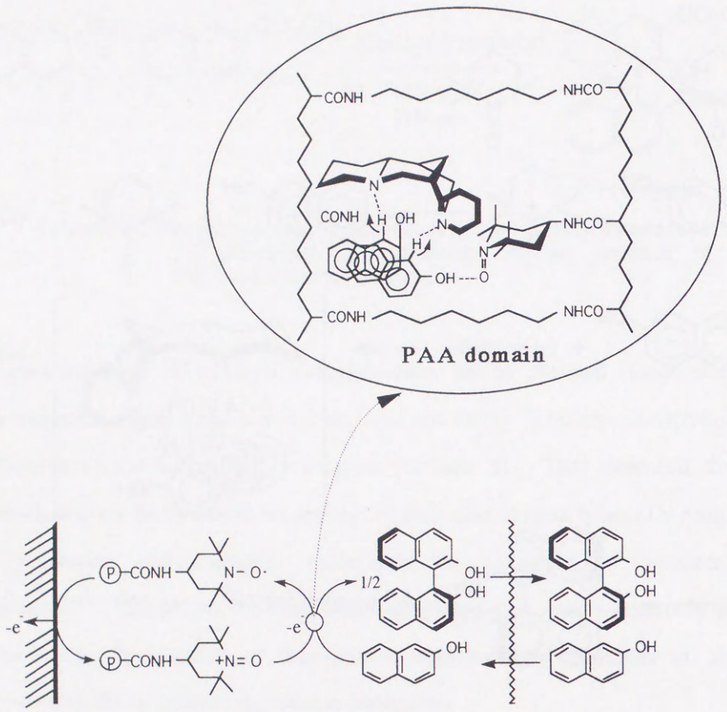
Base on the above discussion, the author would propose the following reaction mechanism as shown in Scheme 6. The oxoammonium ion of TEMPO is formed by one electron oxidation of TEMPO (step i). The electron transfer from **1** to the oxoammonium ion proceeds through the complexation of the oxoammonium ion of TEMPO and **1** (step ii). The two naphthol cations thus formed interact with (-)-sparteine strongly by hydrogen bond in PAA domain bridged by hexamethylenediamine, and the direction of deprotonation from the naphthol cations is controlled by the complex formation (step iii). Two naphthol radicals generated by deprotonation from the naphthol cations couple with each other simultaneously with the formation of naphthol



Scheme 6. A proposed mechanism of stereoselective coupling reaction of 2-naphthol with oxoammonium ion in the presence of (-)-sparteine.

radical, which is the rate-determining step (step iv). The highly enantioselective coupling reactions may be due to a strong interaction between substrate, sparteine and TEMPO moiety in a suitably sized PAA domain formed by the cross-linking with hexamethylenediamine.

Binaphthyl formation seems to proceed via coupling of naphthyl radical,[74] because the electrode is not deactivated during electrolysis. If any TEMPO derivatives



GF Polymer-catalyst layer Solution

Scheme 7. A plausible mechanism of TEMPO-modified GF electrodefor the oxidation of 2-naphthol.

other than oxoammonium ion and TEMPO itself are formed during the coupling reactions, the electrode would be deactivated as in the case of oxidation of alcohols into ketones (which will be described in chapter 4). Biphenanthryl is also formed similarly by one electron oxidation and deprotonation of phenanthrol, where the reaction is

enantiomerically controlled by the strong interaction of phenanthryl radicals with sparteine. The oxidation of **1** in the PAA-catalyst layer of TEMPO-modified PAA-GF electrode is depicted schematically in Scheme 7. In the TEMPO-modified PAA-layer, ternary complex of **1**, (-)-sparteine, and TEMPO residue may be formed through hydrogen bonding as a key intermediate for the induction of chirality.

2-4 Conclusion

The constant potential electrolysis of **1**, **2** and **3** at + 0.6 V *vs.* Ag/AgCl on a TEMPO-modified GF electrode in the presence of (-)-sparteine in acetonitrile yielded (*S*)-binaphthyl type dimers enantioselectively in > 92% isolated yield and >88% current efficiency with the enantiomeric excesses of 98.8, 91.4 and 97% for each dimer, respectively (the values are based on polarimetry). The author believes that the present electrochemical method to synthesize enantioselective coupling products gives the highest values among the enantiomeric yields reported so far. In this context, Nakajima et al. reported that their results of the enantiomeric excess up to 73% is the highest value reported to date for enantioselective oxidative coupling of naphthol derivatives.[86] Nakajima's procedure for the enantioselective oxidative coupling and the TEMPO-base electrocatalytic reactions described in this chapter have a similarity in reaction mechanism in view of the fact that both systems involve an electron transfer in the key step. The author hopes that the electrocatalytic method is widely recognized as one of the useful catalytic methods. Because of the useful features including full consumption of substrate, highly enantioselective product formation, easy isolation of product from reaction mixture, and low consumption of chemical reagent (clean process), this electrocatalytic process is expected to be the simplest and most convenient way to synthesize optically pure binaphthyl and biphenanthryl derivatives from naphthols, naphthyl ethers and phenanthrols.

CHAPTER THREE

Electrocatalytic Lactonization of Methyl-substituted Diols in the Presence of (-)-Sparteine

3-1 Introduction

Optically active substituted lactones have been widey used as building blocks to synthesize biologically active compounds by taking advantage of their chiral and bifunctional nature.[93-97] The preparation of optically pure lactones usually involves a complicated process such as 3-step conversion of methyl (*R*)-(-)-3-hydroxy-2-methyl-propionate to (*S*)-(-)-3,4,5,6-tetrahydro-4-methyl-2-pyranone (*S*-**7**).[98] On the other hand, enzymes have been used successfully for the preparation of optically active lactones directly from substituted diols. The enzyme system of microorganism was also employed for the oxidative formation of such lactones from 1,ω-diols: optically pure (*R*)-(-)-3,4,5,6-tetrahydro-4-methyl-2-pyranone (*S*-**7**) was obtained from 3-methylpentane-1,5-diol (**10**) in 57% yield after 2 d incubation with *Gluconobactor roseus*.[99,100] It is known that TEMPO oxoammonium salts lactonize 1,ω-diols to lactones in a fairly high yield.[101-103] In the TEMPO-catalyzed lactonization, enantioselectivity of substituted lactones which are produced from diols having primary hydroxy and/or secondary hydroxy groups in the molecule has not been controlled.

In this chapter, the author describes a simple electrocatalytic synthetic method of optically pure lactones from methyl-substituted diols on the TEMPO-modified GF electrode in the presence of (-)-sparteine as a chiral deprotonating agent.

3-2 Experimental

Materials.

All chemicals were of commercial products. Dry CH_3CN and $NaClO_4$ were prepared and stored in the same procedures as described in **2-2**.

Cyclic Voltammetry.

Cyclic voltammetry was carried out in a CH_3CN solution containing 0.2 M $NaClO_4$ as supporting electrolyte. The measurement system and conditions were almost the same as those described in **2-2**.

Macroelectrolysis.

Preparative and potential-controlled electrolysis of substrates was carried out using the same cell as used in the previous chapter (Fig. 2). In a typical example, the anolyte contained 1 mmol substrate, 1 mmol tetralin as gas chromatographic standard, 4 mmol (-)-sparteine and 1 mmol $NaClO_4$ as a supporting electrolyte in a total volume of 5 ml. The catholyte was 5 ml CH_3CN solution containing 1 mmol $NaClO_4$. The controlled potential electrolysis was performed at +0.6 V *vs.* Ag/AgCl under a nitrogen atmosphere. The size of the TEMPO-modified GF anode was 1.0 x 1.0 x 0.5 cm^3. The anolyte was sampled at appropriate intervals for GC analysis (CP-Cyclodextrin-B-2,3,6-M-19, 0.25 mm ϕ x 25 m / raising temp. 3 ℃·min^{-1} from 80 to 150 ℃ , inj. temp. 200 ℃, det.c. temp. 240 ℃) and HPLC (CHIRALCEL-OD 0.46 ϕ cm x 25 cm / column temp. 30 ℃, flow speed: 0.5 ml·min^{-1}, solvent: hexane-isopropanol = 95:5). The electrolysis was finished at the time when the substrate disappered on GC or the

electric current diminished. After the electrolysis had been over, the anolyte was evaporated and the residue was dissolved in 30 ml ethyl acetate. The mixture was washed with 0.1 M HCl and H_2O, dried with sodium sulfate and concentrated. Then, the obtained viscous liquid was fed onto a silica gel column (Wako Gel C-200, 3 cm ϕ x 50 cm) and eluted with a hexane-ethyl acetate mixture (9:1 v/v). The eluted solution was evaporated and distilled. The purity of the products was analyzed by GC, HPLC, and polarimeter.

3-3 Results and Discussion

The cyclic voltammograms of 0.2 M 3-methyl-1,5-pentanediol (**10**) on the TEMPO-modified electrode in 0.8 M (-)-sparteine are shown in Fig. 7. In the absence of (-)-sparteine, the oxidation peak current (Fig. 7*b*) was slightly larger than that for

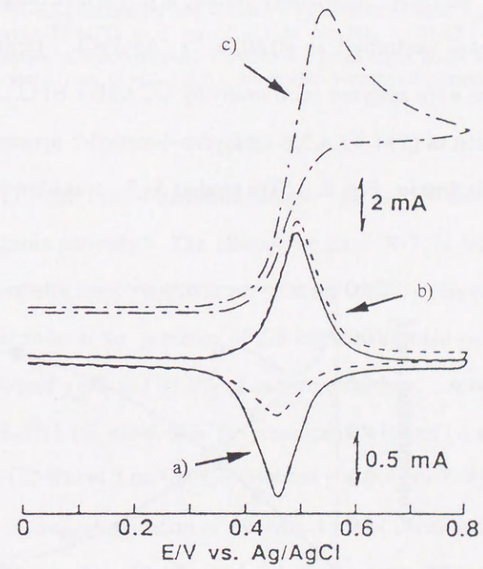


Fig. 7. Cyclic voltammograms on TEMPO-modified GF electrode (1.0 x 1.0 x 0.5 cm^3) in 0.2 M $NaClO_4/CH_3CN$. Scan rate of 10 $mV \cdot s^{-1}$. Curve *a*): in the absence of both 3-methyl-1,5-pentanediol and (-)-sparteine, curve *b*): in the presence of 0.2 M 3-methyl-1,5-pentanediol and in the absence of (-)-sparteine, curve *c*): in the presence of 0.2 M 3-methyl-1,5-pentanediol and 0.8 M (-)-sparteine.

that for blank (Fig. 7*a*, the electrode itself), though the reduction peak current was diminished considerably as compared with that for blank, showing that the oxidation rate of **10** was slow. On the contrary, in the presence of (-)-sparteine, the peak current for **10** was 4.5 fold larger than that for the blank, and no reduction peak was observed (Fig. 7*c*). The phenomena suggest that **10** is electrocatalytically oxidized in the presence of (-)-sparteine.

Based on the cyclic voltammetry results, a preparative electrolysis of 3-methyl-1,5-pentanediol was performed at +0.60 V *vs.* Ag/AgCl. During the electrolysis, aliquots of anolyte were analyzed occasionally by GC and/or HPLC. The consumption of **10** and formation of (*S*)-(-)-3,4,5,6-tetrahydro-4-methyl-2-pyranone (***S*-7**) are plotted against electrolysis time in Fig. 8. The product ***S*-7** was identified by comparing its

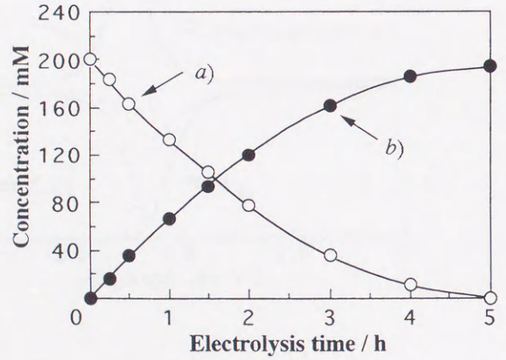


Fig. 8. Macroelectrolysis of 0.2 M 3-methyl-1,5-pentanediol on TEMPO-modified GF electrode (1.0 x 1.0 x 0.5 cm^3) in the presence of 0.8 M (-)-sparteine. Curve *a*): 3-methyl-1,5-pentanediol, curve *b*): *S*-(-)-3,4,5,6-tetrahydro-4-methyl-2-pyranone.

Table 5. Enantioselective Lactonization of 3-Methyl-1,5-pentanediol to (*S*)-(-)-3,4,5,6-Tetrahydro-4-methyl-2-pyranone in the Presence of (-)-Sparteine[a)]

Method	Charge passed / C	Current efficiency / %	Isolated yield / %	$[\alpha]_D^{20}$	*R* : *S*[d)]	ee[d)] / %	Turnover[e)] number
electrocatalytic on TEMPO-modified GF	391.0	92.6	93.8	-26.9°	1.0 : 99.0	98.0	307
electrocatalytic on bare GF[b)]	457.2	77.5	91.8	-0.82°	48.5 : 51.5	3.0	9
reagent oxidation[c)]	—	—	92.3	-0.55°	49.0 : 51.0	2.0	0.9

a) 1 mmol 3-methyl-1,5-pentanediol and 4 mmol (-)-sparteine in each reaction, b) 0.4 mmol 4-acetyl-amino-TEMPO in 5 ml of 0.2 M $NaClO_4$ / CH_3CN, c) 4 mmol oxoammonium tosylate of 4-acetylamino-TEMPO in 5 ml of CH_3CN, 24 h, d) obtained by HPLC, e) calculated from (*S*)-(-)-3,4, 5,6-tetrahydro-4-methyl-2-pyranone (mol) x 2 / TEMPO (mol).

retention time in HPLC with that of authentic sample. In ca. 5 h electrolysis, **10** was converted to ***S*-7** almost perfectly. The electrolysis gave ***S*-7** in 93.8% of isolated yield, 92.6% of current efficiency, and 98% ee. On the contrary, the electrolysis on the TEMPO-modified electrode in the presence of 2,6-lutidine afforded racemic product of (±)-**7** in 94.6% of isolated yield and 91.8% of current efficiency. A bare GF electrode yielded a poor ee of ***S*-7** (3.0% ee) even in the presence of 4 mmol (-)-sparteine and 0.4 mmol 4-acetylamino-TEMPO in 5 ml CH_3CN (isolated yield of (±)-**7**: 91.8% and current efficiency: 77.5%). A reagent oxidation of **10** with 4 mmol oxoammonium tosylate of 4-acetylamino-TEMPO gave **7** in 92.3% yield and (*S*)-isomer in 2% ee. These results are summarized in Table 5. It is clear that the enantioselective oxidation of **10** to ***S*-7** proceeds successfully only on the TEMPO-modified electrode in the presence of (-)-sparteine.

The cyclic voltammograms of the TEMPO-modified electrode after electrolysis are shown in Fig. 9. The peak current of the used electrode decreased to 25 % of the

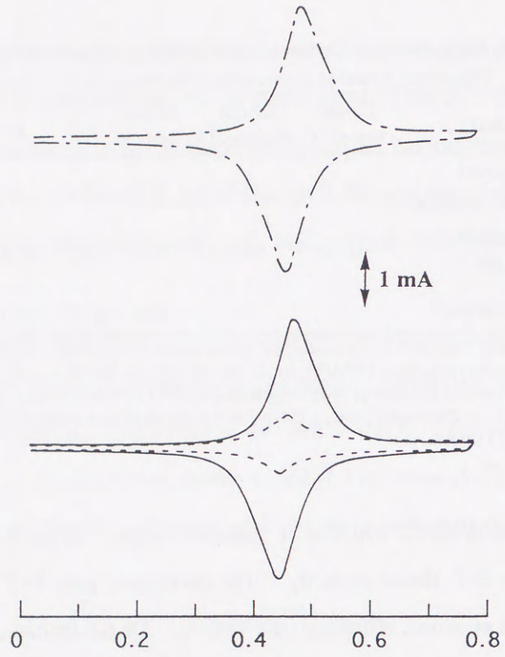


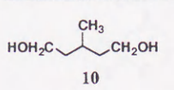
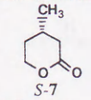
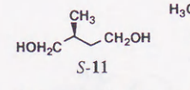
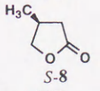
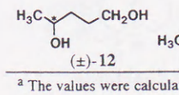
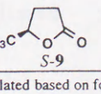
Fig. 9. Cyclic voltammograms at a TEMPO-modified GF electrode (1.0 x 1.0 x 0.5 cm^3) in 0.2 M $NaClO_4/CH_3CN$. Scan rate: 10 mV/s. ———: new electrode, - - - - : inactivated electrodeafter macroelectrolysis, —— - ——: reactivated electrode treated with 10 mM *m*-CPBA / diethyl ether solusion.

original value recorded for new one, suggesting that the electrode was inactivated in part during the electrolysis. For example, an electrocatalytic current of the second run (an additional 1 mmol substrate was added to the electrolyte after the first run of electrolysis) was slightly smaller than that of the first run. However, the electrocatalytic activity of the electrode was recovered completely by the treatment in which the electrode was

immersed in a diethyl ether solution of 10 mM *m*-chloroperbenzoic acid for a day. Since it is known that TEMPO is reduced into its amine form (Scheme 2) by reagent,[104,105] the inactivation of the electrode may be attributable to the formation of amine form of TEMPO which cannot be oxidized electrochemically. Although the detailed mechanism for the deactivation is not clear, it seems that the piperidin-*N*-yloxyl skeleton of TEMPO does not decompose during the electrocatalytic reaction. Furthermore, it was ascertained that (-)-sparteine does not react itself, by the fact that (-)-sparteine was recovered almost quantitatively from the reaction mixture after electrolysis. This fact confirms that (-)-sparteine acts only as a deprotonating agent for alcohols. The protons formed should be reduced at cathode to evolve hydrogen gas. The generation of gas at cathode was actually observed.

The electrolysis of (*S*)-(-)-2-methylbutane-1,4-diol (***S*-11**) and racemic pentane-1,4-diol ((±)-**12**) was carried out on the TEMPO-modified GF electrode under the same

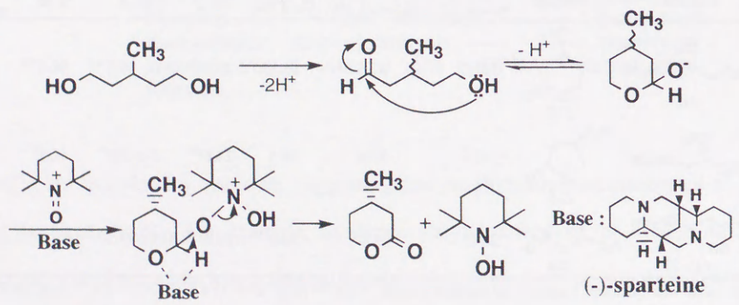
Table 6 Enantioselective Electrocatalytic Lactonization of Methyl-substituted Diols on a TEMPO-modified GF Electroed in the Presence of (-)-Sparteine

Substrate	Product	Charge passed (C)	Current [a] efficiency (%)	Isolated yield (%)	$[\alpha]_D^{20}$	*R* : *S*	% ee	Turnover number
 **10**	 *S*-7	391.0	92.6	93.8	-26.9° [b]	1.0 : 99.0 [e,f]	98.0 [e,f]	307
 *S*-11	 *S*-8	380.9	97.8	96.5	-24.6° [c]	0 : 100 [e]	100 [e]	316
 (±)-**12**	 *S*-9	284.5	65.4	48.2	-29.4° [d]	0.5 : 99.5 [e,f]	99.0 [e,f]	158

[a] The values were calculated based on four electrons process. [b] Lit.[106] $[\alpha]_D^{27}$ -27.6° (*c* 5.6, $CHCl_3$). [c] Lit.[99] $[\alpha]_D^{20}$ -24.7° (*c* 4, CH_3OH). [d] Lit.[107] $[\alpha]_D^{23}$ -29.6° (*c* 1.29, CH_2Cl_2). [e] Measured by GC (CP-Cyclodextrin-B-2,3,6-M-19, 0.25 mm ϕ x 25 m/ raising temp. 3 °C min^{-1} from 80 to 150 °C, inj. temp. 200 °C, detc. temp. 240 °C). [f] Measured by HPLC (CHIRALCEL-OD, 0.46 cm ϕ x 25 cm/column temp. 30 °C, flow speed: 0.5 ml min^{-1}, solvent: hexane-isopropanol = 95:5).

same conditions as for **10** and the results are shown in Table 6. The diol ***S*-11** was similarly oxidized to (*S*)-(-)-4,5-dihydro-4-methyl-2(3*H*)-furanone (***S*-8**) in high current efficiency (97.8%) and isolated yield (96.5%). The optical yield of the lactone was 100%. The use of 2,6-lutidine in place of (-)-sparteine also yielded ***S*-8** in high current efficiency (97.3%) and isolated yield (95.9%). Furthermore, (±)-**12** was electrolyzed on the TEMPO-modified electrode in the presence of (-)-sparteine. In this electrolysis, (*S*)-(-)-4,5-dihydro-5-methyl-2(3*H*)-furanone (***S*-9**) was obtained in 48.2% isolated yield and 99.0% ee. Only the *S*-isomer of (±)-**12** was probably oxidized selectively to yield ***S*-9**.

For the enantioselective lactonization, the following reaction mechanism can be proposed (Scheme 8). As described for the oxidation of naphthols in the previous chapter, diol, (-)-sparteine, and oxoammonium salt of TEMPO interact with each other strongly in a suitable size of PAA domain which is formed by cross-linking with hexamethylenediamine, and the direction of deprotonation from the diol intermediates may be strongly controlled via hydrogen bonds by chiral base in the domain.



Scheme 8. A proposed mechanism of enantioselective lactonization of 3-methyl-1,5-pentanediol with oxoammonium ion in the presence of (-)-sparteine.

3-4 Conclusion

The above results show that the direct electrocatalytic oxidation on the TEMPO-modified GF electrode in the presence of chiral base of (-)-sparteine can be applied for the synthesis of optically pure lactones from prochiral diols and/or chiral diols in enantiomeric excess more than 95%. The present electrocatalytic method possesses many useful features for lactonization, as described in the previous chapter. Therefore, this electrochemical process is expected, in future, to be the simplest and most convenient way to synthesize optically pure lactones which should be valuable for the production of biologically active compounds.

CHAPTER FOUR

Electrocatalytic Oxidation of Racemic Alcohols by Use of Chiral Base

4-1 Introduction

The enantioselective oxidation of racemic alcohols is of high interest for the resolution of optical isomer, and has been carried out by electrochemical method,[108,109] asymmetric epoxidation[110,111] and enzymatic reactions.[106,112] Komori and Nonaka have reported that optically pure (*S*)-(-)-2,2-dimethyl-1-phenyl-1-propanol can be recovered in 43% yield, when racemic 2,2-dimethyl-1-phenylpropanol was oxidized at a poly(L-valine)-coated anode.[108] This is, to the author's knowledge, the first report for electrochemical enantiomer-differentiating reaction. Yamagishi and Aramata also reported the electrooxidative optical resolution of racemic sulfides using Co(1,10-phenanthroline)$_3^{+2}$ complex immobilized in a chiral clay-coated anode.[109] In these reactions, one of the (*R*)- and (*S*)-isomers of racemic substrates is oxidized selectively and then the unreacted isomer can be recovered in optically active form. However, due to the low optical purity of unreacted isomers, these procedures could not be actually applied to optical resolution. The above chemical and enzymatic methods had the follwing drawbacks: use of expensive reagents or enzymes, and a time- and cost-consuming separation of products from the reaction mixture due to the reagents or enzymes.

In this chapter, the author describes an enantioselective oxidation of racemic alcohols on TEMPO-modified GF electrode in the presence of a chiral alkaloid, to provide a simple, clean, and practical process for optical resolution.

4-2 Experimental

Materials

All chemicals were of commercial origin. Dry acetonitrile and anhydrous sodium perchlorate were prepared and stored in the same procedures as described in **2-2.**

Cyclic Voltammetry.

Cyclic voltammetry was carried out in a CH_3CN solution containing 0.2 M $NaClO_4$ as supporting electrolyte. The measurement of voltammograms was carried out according to the procedure described in **2-2**.

Macroelectrolysis.

Preparative and potential-controlled electrolysis of substrates was performed using the same electrolysis cell as used in chapter two (Fig. 2). The anolyte contained 2 mmol substrate, 1 mmol tetralin as gas chromatographic standard, 2 mmol (-)-sparteine and 1 mmol $NaClO_4$ as a supporting electrolyte in a total volume of 5 ml. The catholyte was 5 ml of CH_3CN solution containing 1 mmol $NaClO_4$. The controlled potential electrolysis was carried out at +0.6 V *vs.* Ag/AgCl under a nitrogen atmosphere. The size of the modified anode was 1.0 x 1.0 x 0.5 cm^3. The anolyte was sampled at appropriate intervals for the analysis by GC (CP-Cyclodextrin-B-2,3,6-M-19, 0.25 mm ϕ x 25 m / raising temp. 3 ℃·min^{-1} from 80 to 150 ℃, inj. temp. 200 ℃, detc. temp. 240 ℃) and HPLC (CHIRALCEL-OD 0.46 ϕ cm x 25 cm / column temp. 30 ℃, flow speed: 0.5 ml·min^{-1}, solvent: hexane-isopropanol = 95:5). After the electrolysis had been completed, the anolyte was evaporated and the residue was dissolved in 30 ml of ethyl

acetate. The mixture was washed with 0.1 M HCl and H_2O, dried over sodium sulfate and concentrated. Then, the obtained viscous liquid was purified on a silica gel column (Wako Gel C-200, 3 cm ϕ x 50 cm) using hexane-ethyl acetate mixture (9:1 v/v) as eluent. The eluted solution was evaporated and distilled. The purity of the products was analyzed by GC, HPLC and polarimeter.

4-3 Results and Discussion

The cyclic voltammograms of (*R*)-(+)- and (*S*)-(-)-1-phenylethanol (***R*-13** and ***S*-13**) on the TEMPO-modified electrode in the presence of (-)-sparteine are shown in Fig. 10. The anodic peak current for ***R*-13** (Fig. 10*b*) was slightly larger than that for

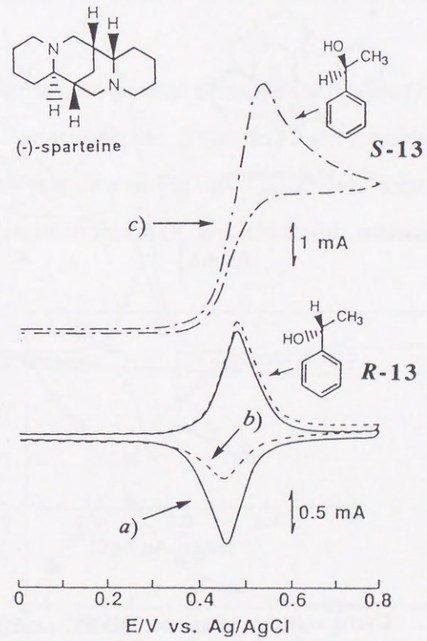


Fig. 10. Cyclic voltammograms on TEMPO-modified GF electrode (1.0 x 1.0 x 0.5 cm^3) in 0.2 M $NaClO_4$ / CH_3CN. Scan rate: 10mV/s. Curve *a*) : in the absence of both (±)-1-phenylethanol and (-)-sparteine (blank experiment), curve*b*): in the presence of 0.2 M (*R*)-(+)-1-phenylethanol and 0.2 M (-)-sparteine, curve *c*): in the presence of 0.2 M (*S*)-(-)-1-phenylethanol and 0.2 M (-)-sparteine.

blank (Fig. 10*a*, the electrode itself), even if (-)-sparteine is present in the electrolyte solution. On the other hand, the anodic peak current for ***S*-13** (Fig. 10*c*) was 2.2 fold larger than that for ***R*-13** and no cathodic peak was observed on the reverse scan, showing that ***S*-13** was oxidized electrocatalytically. The oxidation potential was shifted from 0.47 V to 0.53 V (the oxidation potential of TEMPO-modified electrode

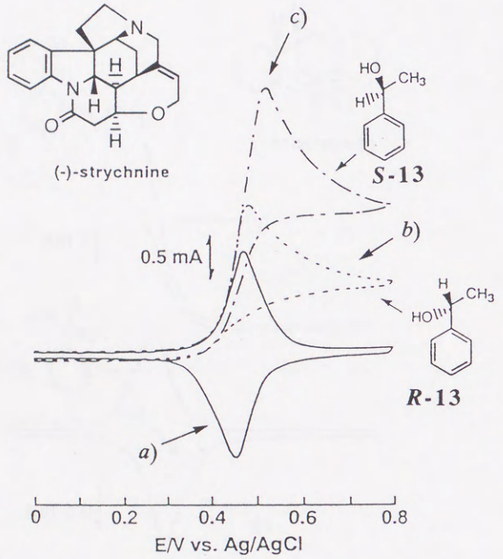


Fig. 11. Cyclic voltammograms on TEMPO-modified GF electrode (1.0 x 1.0 x 0.5 cm^3) in 0.2 M $NaClO_4$ / CH_3CN. Scan rate: 10mV/s. Curve *a*): in the absence of both (±)-1-phenylethanol and (-)-strychnine (blank experiment), curve*b*): in the presence of 0.2 M (*R*)-(+)-1-phenylethanol and 0.2 M (-)-strychnine, curve *c*): in the presence of 0.2 M (*S*)-(-)-1-phenylethanol and 0.2 M (-)-strychnine.

itself). The use of (-)-strychnine instead of (-)-sparteine increased the peak current for ***R*-13** significantly and slightly increased the peak current for ***S*-13** in CVs (Fig. 11). These results suggest that (-)-sparteine is characterized not only by larger electrocatalytic activity than (-)-strychnine but also by higher *S*-enantioselectivity for the racemate **13**. Such characteristics of chiral sparteine were confirmed by the time course of macroelectrolysis of racemic **13** solution in the presence of (-)-sparteine or (-)-strychnine.

A preparative and controlled-potential electrolysis of racemic **13** was performed at +0.60 V vs. Ag/AgCl. The consumption of racemic **13** and formation of acetophenone are plotted against electrolysis time in Fig. 12. ***R*-13** was identified as unreacted alcohol by comparing its retention time of GC and HPLC with authentic sample. After 3

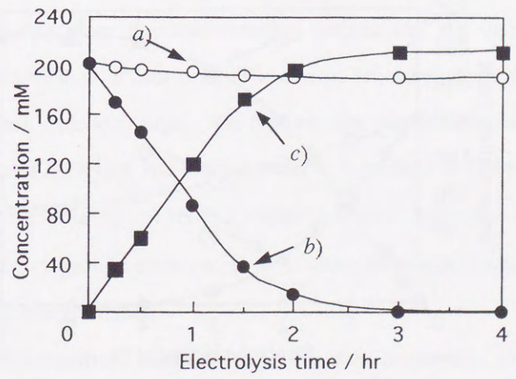


Fig. 12. Macroelectrolysis of 0.4 M (±)-1-phenylethanol on TEMPO-modified GF electrode (1.0 x 1.0 x 0.5 cm^3) in the presence of 0.4 M (-)-sparteine. Curve *a*): (*R*)-(+)-1-phenylethanol, curve *b*): (*S*)-(-)-1-phenylethanol, curve *c*): acetophenone.

h of electrolysis in the presence of (-)-sparteine, ***S*-13** was completely oxidized to acetophenone whereas 92% of ***R*-13** remained unreacted. The current efficiency for the oxidation, the ee of the unreacted alcohol and the turnover number based on TEMPO were 95.1%, 99.6%[113] and 87 respectively. In the presence of (-)-strychnine, ***S*-13** was fully oxidized and 72.2% of ***R*-13** remained unreacted after 4 h of electrolysis (Fig. 13). The current efficiency for the oxidation, ee of the unreacted alcohol and the turnover number of TEMPO were 93%, 95% and 117, respectively. For comparison, the use of 2,6-lutidine afforded non-enantioselectivity for (±)-**13** on the electrode (current efficiency 94.8%, ee 0%, and turnover number 164). A bare GF electrode showed a poor enantioselectivity (***R*-13**, 3.5% ee) in spite of the presence of 2 mmol (-)-sparteine and

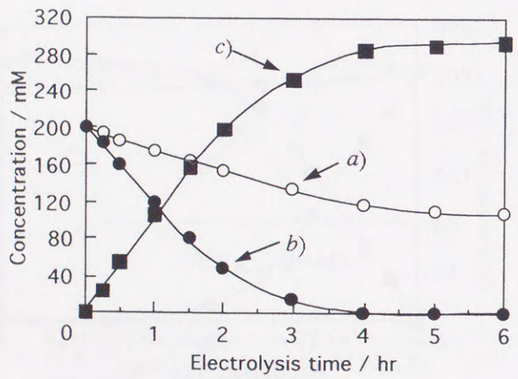


Fig. 13. Macroelectrolysis of 0.4 M (±)-1-phenylethanol on TEMPO-modified GF electrode (1.0 x 1.0 x 0.5 cm^3) in the presence of 0.4 M (-)-strychnine. Curve *a*): (*R*)-(+)-1-phenylethanol, curve *b*): (*S*)-(-)-1-phenylethanol, curve *c*): acetophenone.

Table 7. Comparison of Enantioselective Oxidations of (±)-1-Phenylethanol

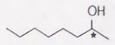
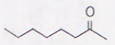
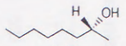
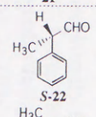
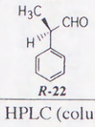
	Modified electrode + (-)-sparteine	Modified electrode + 2,6-lutidine	Bare electrode + (-)-sparteine	$\diagdown N^+=O$ + (-)-sparteine (Homogeneous reaction)
Unreacted (+)-1-phenylethanol (%)	46.2	0	85.3	4.7
ee of *R*-isomer (%)	> 95	0	3.5	2.0
Current efficiency for acetophenone (%)	95.1	94.5	57.3	- - -

0.2 mmol 4-acetylamino-TEMPO in 5 ml CH_3CN (Table 7).

Racemic alcohols of *trans*-2-phenylcyclohexanol ((±)-**14**), 2-octanol ((±)-**15**) and 2-cyclohexen-1-ol ((±)-**16**) were similarly electrolyzed on the TEMPO-modified GF electrode in the presence of (-)-sparteine (Table 8). These racemic alcohols were also *S*-enantioselectively oxidized to the corresponding ketones and the unreacted alcohols contained more than 99% of *R*-isomers. The current efficiency and selectivity for the formation of ketones were also high. On the contrary, the electrooxidation of (±)-2-phenylpropanol ((±)-**17**), which has a chiral center at β-position to hydroxy group, was non-enantioselective (Table 8). This fact means that an α-hydrogen of chiral center adjacent to the hydroxy group seems necessary to attain an enantioselective oxidation in the present electrochemical method.

The TEMPO-modified electrode used for the preparative electrolysis was gradually inactivated during the electrolysis as in the case for lactonization of diols in chapter three. However, the electrocatalytic activity of the electrode was recovered completely by the treatment of the electrode with 10 mM *m*-chloroperbenzoic acid in diethyl ether solution for a day (Fig. 14).

Table 8. Enantioselective Oxidation of Racemic Alcohols on a TEMPO-modified GF Electrode by Use of (-)-Sparteine

Racemic alcohol	Product	Main remained alcohol	Charge passed (C)	Oxidized alcohol (%)	Selectivity of product (%)	Current efficiency (%)	Turnover number	Unreacted alcohol (%)	$[\alpha]_D^{20}$	*R* : *S*	ee (%)
 (±)-**13**	 **18**	 *R*-**13**	53.7	52.9[a]	92.4	95.1	87	46.2[a]	+44° [c]	99.8 : 0.2	99.6
 (±)-**14**	 **19**	 *R*-**14**	56.5	53.8[a]	90.2	91.8	88	45.1[a]	-58° [d]	99.7 : 0.3	99.4
 (±)-**15**	 **20**	 *R*-**15**	52.7	52.1[b]	93.0	95.4	85	46.5[b]	-9.5° [e]	99.8 : 0.2	99.6
 (±)-**16**	 **21**	 *R*-**16**	49.4	50.3[b]	96.4	97.7	82	48.2[b]	+109° [f]	99.9 : 0.1	99.8
 (±)-**17**	 *S*-**22**		101.8	48.9[a]	97.8	92.7	160	0[a]	0°	50.1 : 49.9	0.2
	 *R*-**22**			48.9[a]	97.8			0[a]			

a) Measured by HPLC (column : CHIRALCEL-OD, 0.46 cm ϕ x 25 cm, solvent : hexane:isopropanol= 95:5, flow speed : 0.5ml min^{-1}). b) Measured by GC (column : Cp-Cyclodextrin-B-2,3,6-M-19, 0.25 mm ϕ x 25m, column temp. : raising from 80°C to 150°C, slop : 3°C min^{-1}, inj. temp. : 200°C, detc. temp. : 240°C). c) Compared with authentic sample (Fulka Chemica-Biochemica) : $[\alpha]_D^{20}$ -45±1° (*c* 5, CH_3OH) ; *R* : *S* > 99.5 : 0.5 (GC). d) Compared with authentic sample (Fulka Chemica-Biochemica) : $[\alpha]_D^{20}$ -59±2° (*c* 10, CH_3OH) ; (1*R*,2*S*) : (1*S*,2*R*) > 99 : 1 (GC). e) Lit.[114] $[\alpha]_D^{25}$ -9.9° (neat). f) Lit. [115] $[\alpha]_D^{20}$ +112.0° (*c* 0.60, CH_3Cl).

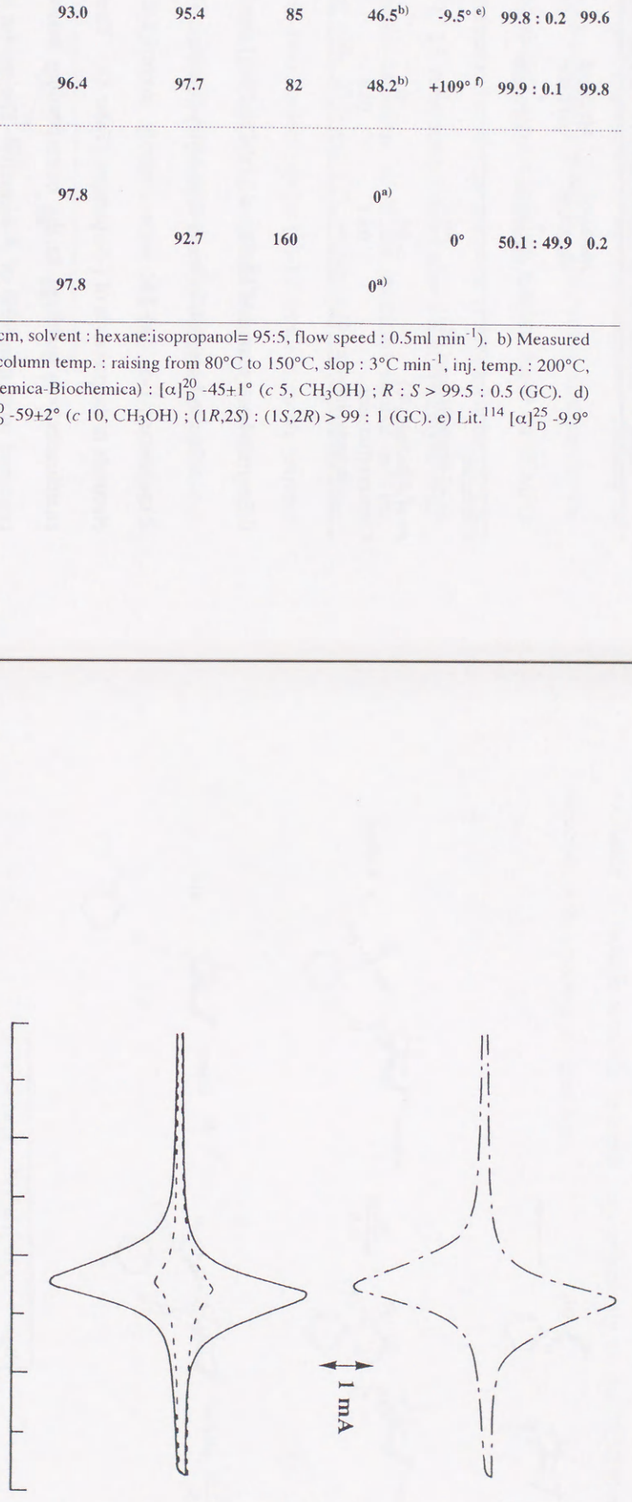
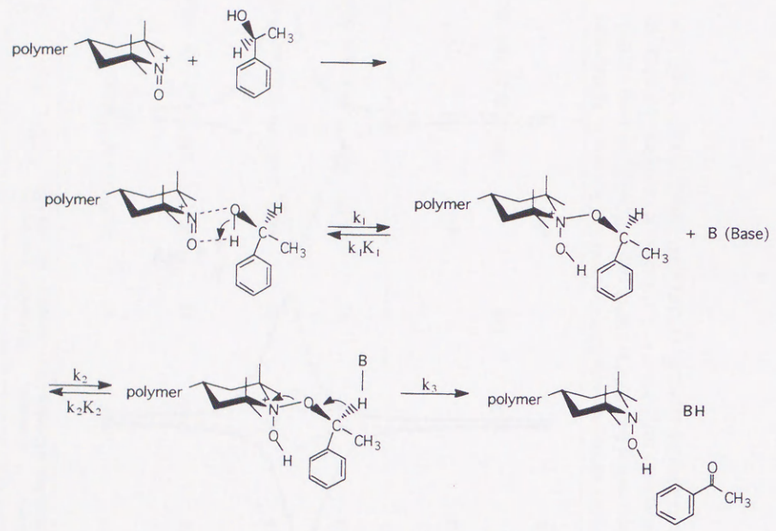


Fig. 14. Cyclic voltammograms at a TEMPO-modified GF electrode (1.0 x 1.0 x 0.5 cm^3) in 0.2 M $NaClO_4/CH_3CN$. Scan rate: 10 mV/s. ——: new electrode, - - - -: inactivated electrode after macroelectrolysis, —— - ——: reactivated electrode treated with 10 mM *m*-CPBA / diethyl ether solusion.

The TEMPO-catalyzed oxidation reaction of alcohols is a two-electron process as shown in Scheme 9. For the enantioselective oxidation, the author proposes the following mechanism (Scheme 9). Substrate, chiral base and oxoammonium salt of TEMPO interact with each other strongly and tightly in a suitably sized PAA domain, and



$D_B \fallingdotseq 1 \times 10^{-5}\ cm^2 \cdot s^{-1}$ $k_1 = 7\ M^{-1}s^{-1}$

$D_s^{app} \fallingdotseq 9 \times 10^{-11}\ cm^2 \cdot s^{-1}$ $k_3 = 14\ s^{-1}$

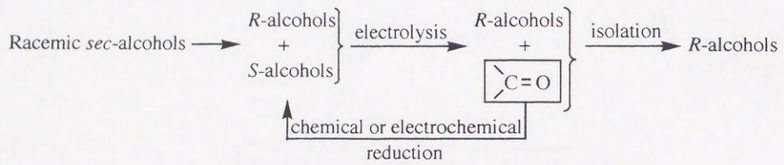
Scheme 9. A proposed mechanism of enantioselective oxidation of 1-phenylethanol with oxoammonium ion in the presence of (-)-sparteine.

electrons are transferred from the substrate to GF electrode via mediator TEMPO. Then, the alcohol was deprotonated by the chiral base with retaining the configuration of the substrate. The higher enantioselectivity was induced by the use of (-)-sparteine than in the case of (-)-strychnine. In any case, it is safe to say that the enantioselective

oxidation of racemic alcohols proceeds very effectively on the TEMPO-modified GF electrode in the presence of chiral base.

4-4 Conclusion

The *S*-isomers of four kinds of racemic alcohols which possess a chiral center at the α-position to the hydroxy group were oxidized to the corresponding ketones on the TEMPO-modified GF electrode in the presence of (-)-sparteine, while the *R*-isomers remained unreacted. The optical purity of the remainning *R*-isomers was > 99% and the current efficiency for the produced ketones was > 90%. The present method, therefore, can provide a valuable electrochemical process for the resolution of racemic alcohols (Scheme 10).



Scheme 10. An electrochemical resolution process of racemic *sec*-alcohols.

CHAPTER FIVE

Conclusion

The preparative electrocatalytic synthesis of some binaphthyls and lactones and the electrocatalytic optical resolution of racemic alcohols using the TEMPO-modified PAA-coated GF electrode have resulted in high chemical yield, high current efficiency, and high enantioselectivity. These satisfactory results are based on the suitable combination of graphite felt, PAA, and TEMPO as electrode material, reaction and electron transfer field, and electron mediator, respectively. Some characteristics of GF and TEMPO were described in chapter one. Polymer coated electrodes have been studied widely and found many applications.[116,117] In the early stage of the study, researchers used polypyrrole very frequently for their easy preparation. However, the polypyrrole-modified electrodes were found to be ineffective for the purpose of praparative electrosynthesis. A densely-packed nature of the polypyrrole chains may be responsible for unpopularity of this material for synthetic purpose. On the other hand, PAA has many favorable properties in the preparation of polymer-coated electrodes: a) easy control of the layer thickness by dip-coating from a PAA/methanol solution, b) strong adsorption to electrode surface, particularly, to GF surface, c) easy modification of PAA layer through the carboxyl groups, d) precise control of hydrophilicity or lipophilicity by regulating the content of free carboxyl residues, e) organic compounds can be condensed into a lipophilic PAA layer from the bulk solution, f) an appropriate size of domain can be prepared by cross-linking, where activated complexes can be formed, and g) a high chemical stability of PAA layer. The item f) would be very important to achieve enantioselective synthesis, though the domain structure of PAA has not been characterised in detail.

The enantioselectivity attained in this study, to the author's knowledge, is one of the highest values reported so far for the enantioselective reactions based on chemical,

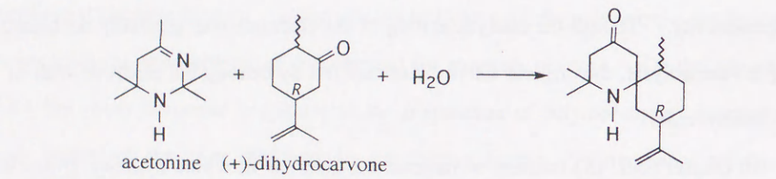
catalytic, and electrochemical methods. In chapter two, napthol, naphthyl ether and phenanthrol were converted to the corresponding optically pure (*S*)-binaphthyl type dimers on the TEMPO-modified GF electrode in the presence of (-)-sparteine as a chiral deprotonating agent in high isolated yield, high current efficiency, and high enantioselectivity. During the electrolysis, the electrode was stable and held its electrocatalytic activity in oxidation, which made it possible to use the electrode repeatedly.

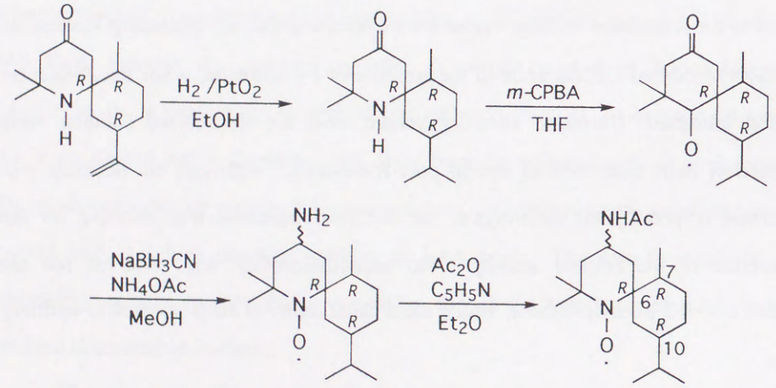
In chapter three, prochiral diols and (*S*)-chiral diols were converted to the corresponding optically pure (*S*)-lactones on the TEMPO-modified GF electrode in the presence of (-)-sparteine in high isolated yield, high current efficiency, and high enantioselectivity. Though the catalytic activity of the electrode was gradually decreased during the electrolysis, the original activity was restored by treating the electrode with *m*-CPBA/diethyl ether.

In chapter four, (*S*)-isomers of racemic sec-alcohols in which hydroxy group is attached to the α-position to chiral center were oxidized to the corresponding ketones on the TEMPO-modified GF electrode in the presence of (-)-sparteine, while the *R*-isomers remained unreacted. Unreacted alcohols isolated from the electrolyzed solution were composed of more than 99% of optical pure *R*-isomers. Although the electrode was deteriorated in part by the electrolysis, the *m*-CPBA treatment was effective for the reproduction of the original activity. No enantioselectivity was observed for the oxidation of (±)-2-phenylpropanol, which has a chiral center at the β-position to hydroxy group.

In order to establish more effective systems for the enantioselective reactions, an appropriate choice of chiral base would be of crucial importance. It was described in

chapter two that the enantioselectivity of the oxidative coupling reaction of 2-naphthol is reversed into (*S*)-selectivity by the use of (-)-brucine as compared with (*R*)-selectivity induced by (-)-sparteine. These results suggest a possibility to regulate the enantio-selectivity of the reaction by changing the type of chiral base. In this context, one should pay attention to the fact that chiral base sometimes is sensitive to air in the electrolytic solution, as is the case for (-)-sparteine. A possible way to circumvent this problem is to use a chiral TEMPO-modified electrode in the presence of stable achiral base such as 2,6-lutidine. In fact, among many kinds of chiral nitroxides[105,118-125], (6*R*, 7 *R* , 10 *R*)-4-acetylamino-1-aza-10-isopropyl-1-oxo-2,2,7-trimethylspiro[5.5]undecane





Scheme 11. Synthesis of Chiral-TEMPO (6*R*,7*R*,10*R*)-4-acetylamino-1-aza-10-isopropyl-1-oxo-2,2,7-trimethylspiro[5.5]undecane.

(Scheme 11) has been used as chiral oxidant for the oxidation of 1-phenylethanol in homogeneous system.[125] The chiral TEMPO oxidizes *S*-isomer 5 times faster than *R*-isomer of racemic 1-phenylethanol in solution. Such chiral TEMPO is expected to be immobilized on the electrode surface to fabricate chiral TEMPO-modified GF electrodes, on which enantioselective reactions can be carried out using a stable base.

The present study on the mediator TEMPO-modified electrodes provides not only many applications to the enantioselective oxidation reactions, but will find out a new type of enantioselective reactions. The author expects a further development of this kind of advanced electrochemical methods as a new methodology in organic synthesis.

References and Notes

1) H. L. F. von Helmholtz, *Ann. Physik.*, [2] **89**, 211 (1858).

2) G. Quincka, *Pagg. Ann.*, **113**, 513 (1861).

3) R. Parsons, "Modern Aspects of Electrochemistry," Vol. I, pp. 103~179, J. O'M. Bockris, ed., Butterworths, London (1954).

4) P. Delahay, "Double Layer and Electrode Kinetics," Interscience, New York (1965).

5) R. Tamamushi, "Fundamentals of Electrode Reaction," pp. 1~30, T. Osa, ed., Kyouritsu Shuppan, Tokyo (1973).

6) A. N. Frumkin, *Trudy Khim. Inst. L. Ya. Karpova*, **4**, 56 (1925).

7) Many review articles and books have been published. For example, S. G. Mairanovskii, "Catalytic and Kinetic Waves in Polarography," Chapt. 3, pp. 57~114, Plenum, New York (1968).

8) J. P. Carr and N. A. Hamon, *Chem. Rev.*, **72**, 679 (1972).

9) G. R. Clemo and J. M. Smith, *J. Chem. Soc.*, **1928**, 2423.

10) T. Osa, *Sekiyugakkaishi*, **19**, 63, (1976).

11) (a) H. Dahms and M. Green, *J. Electrochem. Soc.*, **110**, 1075 (1963). (b) J. O'M. Bockris, M. Green, and D. A. J. Swinkels, *J. Electrochem. Soc.*, **111**, 743 (1964). (c) X. de Hemptinne, *Ann. Soc. Sci. Bruxelles*, **80**, 140 (1996).

12) T. Nonaka, "Organic Electrochemistry," Chapt. 27, pp. 1131~1195, H. Lund and M. M. Baizer ed., Marcel Dekkar, New York (1991).

13) R. N. Gourley, J. Grimshaw, and P. G. Millar, *Chem. Commun.*, **1967**, 1278.

14) R. N. Gourley, J. Grimshaw, and P. G. Millar, *Chem. Commun.*, **1970**, 2318.

15) E. Raoult, J. Sarrazin, and A. Tallec, *Bull. Soc. Chim. Fr.*, **II**, 420 (1981).

16) E. Kariv, H. A. Terni, and E. Gileadi, *J. Electrochem. Soc.*, **120**, 639 (1973).

17) E. Kariv, H. A. Terni, and E. Gileadi, *Electrochim. Acta*, **18**, 433 (1973).

18) M. Jubault, E. Raoult, and D. Peltier, *Electrochim. Acta*, **19**, 865 (1974).

19) M. Jubault, E. Raoult, and D. Peltier, *Electrochim. Acta*, **21**, 407 (1976).

20) J. Hermolin, J. Kopilov, and E. Gileadi, *J. Electroanal. Chem.*, **71**, 245 (1976).

21) J. Kopilov, E. Kariv, and L. L. Miller, *J. Am. Chem. Soc.*, **99**, 3450 (1977).

22) K. Koster, P. Piemenschneider, and H. Wendt, *Israel J. Chem.*, **18**, 141 (1979).

23) H. Wendt, *Angew. Chem., Int. Ed. Engl.*, **21**, 256 (1982).

24) K. Koster and H. Wendt, *J. Electroanal. Chem.*, **138**, 209 (1982).

25) K. Koster and H. Wendt, *J. Electroanal. Chem.*, **157**, 113 (1983).

26) M. Jubault, E. Raoult, and D. Peltier, *Electrochim. Acta*, **25**, 1359 (1980).

27) M. Jubault, *J. Chem. Soc., Chem. Commun.*, **1980**, 953.

28) N. Schoo and H.-J. Schafer, *Liebigs Ann. Chem.*, **1993**, 601.

29) U. Howeler, N. Schoo, and H.-J. Schafer, *Liebigs Ann. Chem.*, **1993**, 609.

30) M. Jubault and E. Raoult, *J. Chem. Soc. Chem. Commun.*, **1977**, 250.

31) M. Jubault, E. Raoult, and D. Peltier, *J. Chem. Soc., Chem. Commun.*, **1979**, 232.

32) M. Jubault, A. Lebouc, and A. Tallec, *Elecrtochim. Acta*, **27**, 1339.

33) R. Hazard, S. Jaouannet, and A. Tallec, *Tetrahedron Lett.*, **1979**, 1105.

34) R. Hazard, S. Jaouannet, and A. Tallec, *Tetrahedron*, **38**, 93 (1982).

35) A. Tallec, R. Hazard, A. Le Bouc, and J. Grimshaw, *J. Chem. Res. (S)*, **1986**, 342.

36) R. Bennes, M. Jubault, M. Privat, and P. Vanel, *Electrochim. Acta*, **26**, 1079 (1981).

37) E. Tronel-Peyroz and D. Schuhmann, *J. Electroanal. Chem.*, **129**, 265 (1981).

38) J. Sarrazin, J. Simonet, and A. Tallec, *Electrochim. Acta*, **27**, 1763 (1982).

39) K. Koster, H. Wendt, and A. Lebouc, *J. Electroanal. Chem.*, **157**, 89 (1983).

40) T. Nonaka, Y. Kumai, M. Ito, and T. Fuchigami, *Asahi Glass Found. Res. Rep.*, **32**, 155 (1978); *Chem. Abstr.*, **91**, 98972v (1979).

41) L. Horner and D. Degner, *Tetrahedron Lett.*, **1968**, 5889.

42) L. Horner and D. Degner, *Tetrahedron Lett.*, **1971**, 1245.

43) L. Horner, D. Degner, and D. Skaletz, *Chem. Eng. Tech.*, **44**, 209 (1972).

44) L. Horner and R. Schnedier, *Tetrahedron Lett.*, **1973**, 3133.

45) L. Horner and D. Degner, *Electrochim. Acta*, **19**, 611 (1974).

46) D. Brown and L. Horner, *Liebigs Ann. Chem.*, **1977**, 77.

47) L. Horner and W. Brich, *Liebigs Ann. Chem.*, **1978**, 710.

48) L. Horner and W. Brich, *Chem. Ber.*, **111**, 574 (1978).

49) W. J. M. van Tilborg and C. J. Smit, *Rec. J. Roy. Netherl. Chem. Soc.*, **97**, 89 (1978).

50) L. Horner and D. H. Skaletz, *Tetrahedron Lett.*, **1970**, 3679.

51) L. Horner and D. H. Skaletz, *Liebigs Ann. Chem.*, **1977**, 1365.

52) D. Seebach and H. A. Oei, *Angew. Chem. Int. Ed. Engl.*, **14**, 634. (1975).

53) D. Seebach, H. A. Oei, and H. Daum, *Chem. Ber.*, **110**, 2316 (1977).

54) B. F. Watkins, J. R. Behling, E. Kariv, and L. L. Miller, *J. Am. Chem. Soc.*, **97**, 3549 (1975).

55) B. E. Firth, L. L. Miller, M. Mitani, T. Rogers, J. Lennox, and R. W. Murray, *J. Am. Chem. Soc.*, **98**, 8271 (1976).

56) B. E. Firth and L. L. Miller, *J. Am. Chem. Soc.*, **98**, 8272 (1976).

57) L. Horner and W. Brich, *Liebigs Ann. Chem.*, **1977**, 1354.

58) A. Abe, T. Nonaka, and T. Fuchigami, *J. Am. Chem. Soc.*, **105**, 3630 (1983).

59) T. Nonaka, S. Abe, and T. Fuchigami, *Bull. Chem. Soc. Jpn.*, **56**, 2778 (1983).

60) S. Abe, T. Fuchigami, and T. Nonaka, *Chem. Lett.*, **1983**, 1033.

61) S. Abe and T. Nonaka, *Chem. Lett.*, **1983**, 1541.

62) T. Komori and T. Nonaka, *J. Am. Chem. Soc.*, **105**, 5690 (1983).

63) T. Komori and T. Nonaka, *J. Am. Chem. Soc.*, **106**, 2656 (1984).

64) A. Yamagishi and A. Aramata, *J. Electroanal. Chem.*, **191**, 449 (1985).

65) J. Berthelot, M, Jubault, and J. Simonet, *Electrochim. Acta*, **28**, 1719 (1983).

66) The first paper in this area is; M. Fujihira, T. Matsue, and T. Osa, *Chem. Lett.*, **1976**, 875.

67) The first paper in this area is; T. Matsue, M. Fujihira, and T. Osa, *J. Electrochem. Soc.*, **126**, 500 (1979).

68) M. Fujihira, A. Yokozawa, H. Kinoshita, and T. Osa, *Chem. Lett.*, **1982**, 1089.

69) T. Osa, T. Matsue, A. Yokozawa, T. Yamada, and T. Fujihira, *Denki Kagaku*, **53**, 104 (1985).

70) T. Osa, U. Akiba, I. Segawa, and J. M. Bobbitt, *Chem. Lett.*, **1988**, 1423.

71) Y. Kashiwagi, H. Ono, and T. Osa, *Chem. Lett.*, **1993**, 257.

72) T. Osa, Y. Kashiwagi, K. Mukai, A. Ohsawa, and J. M. Bobbitt, *Chem. Lett.*, **1990**, 75.

73) Y. Kashiwagi, A. Ohsawa, T. Osa, Z. Ma, and J. M. Bobbitt, *Chem. Lett.*, **1991**, 581.

74) Y. Kashiwagi, H. Ono, and T. Osa, *Chem. Lett.*, **1993**, 81.

75) L. Papouchado, R. W. Sandford. G. Petrie, and R. N. Adams, *J. Electroanal. Chem.*, **65**, 275 (1975).

76) C. Rosini, L. Franzini, A. Raffaelli, and P. Salvadori, *Synthesis*, **1992**, 503.

77) K. Narasaka, *Synthesis*, **1991**, 1.

78) S. Miyano, M. Tobita, and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, **54**, 3522 (1981).

79) A. I. Meyers and K. A. Lutomsky, *J. Am. Chem. Soc.*, **104**, 879 (1982).

80) J. M. Wilson and D. J. Cram, *J. Am. Chem. Soc.*, **104**, 881 (1982).

81) Y. Yamamoto, H. Fukushima, and M. Nakazaki, *J. Chem. Soc., Chem. Commun.*, **1984**, 1490.

82) J. Brussee, J. L. C. Groenendijk, J. M. Koppele, and A. C. A. Jansen, *Tetrahedron*, **41**, 3313 (1985).

83) M. Smrcina, M. Lorenc, V. Hanus, P. Sedmera, and P. Kocovsky, *J. Org. Chem.*, **57**, 1917 (1992).

84) M. Smrcina, J. Polakova, S. Vyskocil, and P. Kocovsky, *J. Org. Chem.*, **58**, 4534 (1993).

85) M. Noji, M. Nakajima, and K. Koga, *Tetrahedron Lett.*, **35**, 7983 (1994).

86) M. Nakajima, K. Kanayama, I. Miyosi, and S. Hashimoto, *Tetrahedron Lett.*, **36**, 9519 (1995).

87) J. A. Riddick and W. B. Bunger, "*Techniques of Chemistry Vol. II, Organic Solvent*", John Willey & Sons, Inc., New York (1970).

88) F. H. Stodola, *J. Org. Chem.*, **29**, 2409 (1964).

89) (a) J. H. Osiecki and E. F. Ullman, *J. Am. Chem. Soc.*, **90**, 1078 (1968).
(b) D. G. B. Boocock and E. F. Ullman, *J. Am. Chem. Soc.*, **90**, 6873 (1968).

90) The reagent was prepared by the reaction of 4-acetylamino-TEMPO with *p*-toluene-sulfonic acid monohydrate in CH_2Cl_2 according to the literature : Z. Ma and J. M. Bobbitt, *J. Org. Chem.*, **56**, 6110 (1991).

91) J. M. Bobbitt has been developing some phenol coupling reactions with this reagent. For instance, J. M. Bobbitt and Z. Ma, *Heterocycles*, **33**, 641 (1992).

92) M. F. Semmelhack and C. R. Schmid, *J. Am. Chem. Soc.*, **105**, 6732 (1983).

93) M. Schmid and R. Barner, *Helv. Chim. Acta*, **62**, 464 (1979).

94) S. Suzuki, F. Mori, T. Takigawa, K. Ibata, Y. Ninagawa, T. Nishida, M. Mizuno, and Y. Tanaka, *Tetrahedron Lett.*, **24**, 5103 (1983).

95) F. E. Zieger, W. T. Cain, A. Kneisley, E. P. Stirchak, and R. T. Wester, *J. Am. Chem. Soc.*, **110**, 5434 (1988).

96) F. E. Zieger, W. T. Cain, A. Kneisley, E. P. Stirchak, and R. T. Wester, *J. Am. Chem. Soc.*, **110**, 5442 (1988).

97) F. E. Ziegler and W. T. Cain, *J. Org. Chem.*, **54**, 3347 (1989).

98) K. Mori, *Tetrahedron*, **39**, 3107 (1983).

99) H. G. W. Leuenberger, W. Boguth, R. Barner, M. Schmidt, and R. Zell, *Helv. Chim. Acta*, **62**, 455 (1979).

100) H. Ohta, H. Tetsukawa, and N. Noto, *J. Org. Chem.*, **47**, 2400 (1982).

101) T. Miyazawa and T. Endo, *J. Org. Chem.*, **50**, 3930 (1985).

102) T. Inokuchi, S. Matsumoto, T. Nishiyama, and S. Torii, *J. Org. Chem.*, **52**, 2559 (1987).

103) P. L. Anelli, S. Banfi, F. Montanari, and S. Quici, *J. Org. Chem.*, **54**, 2070 (1989).

104) E. G. Rozantsev and V. D. Sholle, *Synthesis*, **1971**, 190.

105) J. S. Roberts and D. Thomson, *J. Chem. Soc., Perkin Trans. 2*, **1972**, 2129.

106) A. J. Irwin and J. B. Jones, *J. Am. Chem. Soc.*, **99**, 1625 (1977).

107) K. Mori, *Tetrahedron*, **31**, 3011 (1975).

108) T. Komori and T. Nonaka, *Chem. Lett.*, **1984**, 509.

109) A. Yamagishi and A. Aramata, *J. Chem. Soc., Chem. Commun.*, **1984**, 452.

110) V. S. Martin, S. S. Woodward, T. Katsuki, Y. Yamada, M. Ikeda, and K. B. Sharpless, *J. Am. Chem. Soc.*, **103**, 6237 (1981).

111) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, and K. B. Sharpless, *J. Am. Chem. Soc.*, **109**, 5765 (1987).

112) L. G. Lee and G. M. Whitesides, *J. Am. Chem. Soc.*, **107**, 6999 (1985).

113) Compared with authentic sample (Fulka Chemica-Biochemica) : $[\alpha] = +45\pm1°$ (*c* 5, CH_3OH); *R* : *S* > 99.5 : 0.5 (GC).

114) Y. Y. Lin, D. N. Palmer, and J. B. Jones, *Can. J. Chem.*, **52**, 469 (1973).

115) R. K. Hill and W. Morgan, *J. Org. Chem.*, **33**, 927 (1968).

116) Many reviews have been published. For instance, N. Oyama and H. Matsuda, *Denki Kagaku*, **49**, 396 (1981).

117) K. Itaya and A. J. Bard, *Anal. Chem.*, **50**, 1487 (1978).

118) (a) H. G. Aurich, "in Nitrones, Nitronates and Nitroxides", ed. S. Patai and Z. Rappoport, John Willey & Sons, Inc., New York, pp. 313-399 (1989). (b) M.E. S. Kagan, V. I. Mikhailov, E. G. Rozantsev, and V. D. Sholle, *Synthesis*, **1984**, 895. (c) J. F. W. *Keana, Chem. Rev.*, **78**, 37. (1978). (d) E. G. Rozantsev, and V. D. Sholle, *Synthesis*, **1971**, 401. (e) L. B. Volodarsky, "Imidazoline Nitroxides", CRC Press, Boca Raton, FL, Vols. 1 and 2 (1988).

119) P. Y. Brunel, H. Lemaire, and A. Rassat, *Bull. Soc. Chim. Fr.*, **1964**, 1895.

120) C. Berti and M. J. Perkins, *Angew. Chem. Int. Ed. Engl.*, **18**, 864 (1979).

121) R. Ramasseul and A. Rassat, *Tetrahedron Lett.*, **1971**, 4623.

122) A. Collat, J. Jacques, B. Chion, and J. Lajzerowicz, *Tetrahedron*, **31**, 2243 (1975).

123) K. Flohr, R. M. Paton, and E. T. Kaiser, *J. Am. Chem. Soc.*, **97**, 1209 (1975).

124) (a) H. O. Hankovszky, K. Hideg, M. J. Lovas, B. Jerdovich, A. Rockenbauer, M. Gyor, and P. Sohara, *Can. J. Chem.*, **67**, 1392 (1989). (b) J. F. W. Keana and V. S. Prabhu, *J. Org. Chem.*, **51**, 4300 (1986). (c) J. F. W. Keana, G. S. Heo, and G. T. Gaughan, *J. Org. Chem.*, **50**, 2346 (1985). (d) J. F. W. Keana, S. E. Seyedrezai, and G. T. Gaughan, *J. Org. Chem.*, **48**, 2644 (1983).

125) Z. Ma, Q. Huang, and J. M. Bobbitt, *J. Org. Chem.*, **58**, 4837 (1993).